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BASOPHILIC HYPERPLASIA OF THE PITUITARY IN ESSENTIAL HYPERTENSION.

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Hypertension unassociated with renal disease or serious arterial change has been long the object of etiologic debate. There is growing evidence to demonstrate a close relationship between the endocrine glands and this form of hypertension. A recent survey[1] of the rôle played by the adrenals brings forcibly to the fore that hyperplasia of these organs, as well as certain of their neoplasms, is accompanied by a hypertension, either continual or paroxysmal in type. A hyperadrenalism as a cause for hypertension has been treated successfully with partial bilateral suprarenalectomy.

On the other hand, a careful study of the basophilic pituitary syndrome will show that an adenoma of the adrenal cortex or a hyperplasia of the gland was also found in many of these cases. Likewise injections of pituitary extracts will bring about hypertrophy of the suprarenal cortex. Moehlig and Osius,[2] Smith[3] and others have stressed the fact that both the pituitary and suprarenal cortex reflect the state of each other and that the pituitary is probably the dominant gland.

The syndrome of pituitary basophilism, as first reported by Cushing,[4] indicated that hypertension was an outstanding sign. These cases with verified basophil adenomas of the anterior lobe of the hypophysis all showed a uniform symptomatology. Others also described by him, although unverified pathologically, presented the characteristic syndrome of amenorrhea or impotence, hypertrichosis, hypertension, obesity, purplish lineæ atrophicæ on the abdomen or thighs, polycythemia, plethora, osteoporosis, etc.

The pattern shown in these cases was immediately recognized by other observers. A number of variations were reported by me[5] as appearing in patients—unverified clinical cases—all of whom presented many, if not all, of the classical signs of this condition. Williams[6] also reported a patient 66 years of age in whom there was a psychosis of the senile type, a carcinoma, hypertension, polycythemia, purpuric spots with plethoric facies and a marked masculine hypertrichosis, but confirmation of basophilism was not verified.

In a later communication Cushing[7] made an interesting suggestion as to the additional importance of the basophil cells, in connection with a case of fatal eclampsia in which there was found a hyperplasia of basophil cells which were invading the posterior lobe. He[8] noted that the fully ripened elements of the pars intermedia are indistinguishable from the basophil cells of the pars anterior and that they secrete the active hormone of the posterior lobe. Massive basophilic invasion is nothing more than an exaggeration of the normal secretory process and he feels it is a reasonable explanation of the symptoms which accompany basophilic adenoma and the symptomatically related states of eclampsia and essential hypertension. This he considers is brought about by an activation of the posterior lobe by the basophilic elements. As additional evidence he cites Hofbrauer and Anselmino, who demonstrated an excess of posterior lobelike substance (antidiuretic and hemodynamic) in the blood of patients with a hypertensive form of eclampsia.

These observations and the occurrence of pluriglandular cases with only a few signs of the basophilic syndrome had led me to feel that many cases could be found in whom a basophil adenoma could not be proven, but who undoubtedly presented in part the clinical syndrome of pituitary basophilism. Following are 2 case reports which demonstrate strikingly this syndrome.

Case Abstracts. CASE 1.—C.M. (Fig. 1), male, aged 32, was admitted to the surgical ward, St. Luke's Hospital, December 26, 1933, because he had felt something snap in his chest while he was lifting a bookcase on the previous day. Several hours after the accident he coughed up some blood. He had been examined 3 years previously for life insurance and at that time was found to have diabetes. On admission to the hospital he had slight polyphagia, polydipsia and nocturia. There was some impotence. For many years he had suffered off and on from headaches located bifrontally and parietal. Examination and Roentgen ray studies revealed a fracture of the sixth, seventh, eighth and ninth ribs. He was then transferred to the medical service of Dr. L. F. Frissell where a complete survey of his condition was made.

Physical examination showed a man of medium height, plethoric and ruddy, with slight exophthalmos. He was rather obese with marked abdominal adiposity. The thyroid was not palpable and the hands were short with rather square fingers. The hair growth was profuse, with heavy eyebrows and beard and marked hypertrichosis on limbs and abdomen (Fig. 2). On the abdomen below the navel were purpuric lineæ atrophicæ radiating from the base of the pubes up over the abdomen with some striæ also on the thighs and transverse in the suprailiac region. Eye grounds

(Dr. A. Wiener) showed a blurred optic disk with tortuous arteries and hemorrhages scattered through the retina—the characteristic picture of a diabetic retinitis. The visual fields were normal. The blood pressure was 180/130. The laboratory examinations were as follows: Hemoglobin, 110%; red cells, 4,700,000; white cells, 12,600; neutrophils, 90%. The urine showed a specific gravity of 1.006, faint trace of albumin and no sugar, acetone or diacetic acid. The blood sugar showed 165 mg. per 100 cc.; calcium, 10.3 mg.; phosphorus, 2.6 mg. The blood sugar curve was 125–250–308–200–167 mg. The urine sugar the second hour was 1.05 gm.; the fourth hour, 2.15 gm.; the sixth hour, 0.56 gm., and the eighth hour, negative. The basal metabolic rate was −23%. There were no changes in the spinal

FIG. 1.—Case 1 showing slight exophthalmos, hirsuties and abdominal striæ.

fluid. Roentgen rays of the skull showed the sella turcica to be of average size. There was no erosion. The frontal sinuses were small and a mottling and granular appearance of the skull throughout was noteworthy. Through the basal region and the sella there was a thinning out of the bone. Anteriorly, the bones presented a finely granular appearance which suggested a loss of calcium.

A second admission on March 24, 1934, was necessary because of swelling of the ankles and increasing dyspnea. At this time examination revealed flushed plethoric facies with slight exophthalmos; the heart was enlarged and there was a systolic murmur at the apex and an accentuated aortic second sound. The blood pressure was 180/140; the liver was enlarged 3 inches below the costal margin and was tender. The eye grounds showed

hyperemic disk with spots of degeneration and exudate. The fields were normal. Laboratory examinations revealed urea nitrogen, 17 mg.; sugar, 286 mg.; CO_2, 52%. The Wassermann test was negative. The specific gravity of the urine was 1.008; there was a trace of albumin; 3% sugar; no acetone or diacetic acid and occasional hyalin and granular casts. Radiation of the pituitary was recommended on April 4, 1934, and 4 treatments were given during which time the patient was relatively well and allowed to go home. He remained in this state until 4 days before his third admission—June 15, 1934. On admission there was cyanosis, Cheyne-Stokes breathing, plethoric facies, abdominal striæ, hypertrichosis of the body, small genitalia. There were fine and coarse râles in the lungs and roughened

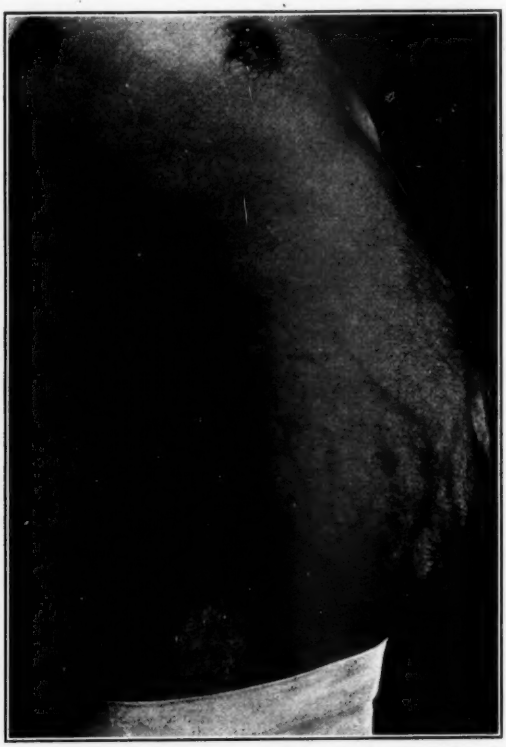

FIG. 2.—Case 1, demonstrating abdominal adiposity with purplish lineæ atrophicæ.

breath sounds. An electrocardiogram at this time demonstrated myocardial damage. The blood pressure was 195/125. The basal metabolic rate was −16 and −25%. The blood count was normal. The blood chemistry showed the urea nitrogen, 22.7 mg.; uric acid, 6.4 mg.; creatinin, 1 mg.; sugar, 285 mg.; CO_2, 46.6%. On July 6, the urea nitrogen was 15.7 mg.; sugar, 125 mg.; CO_2, 37.4%; uric acid, 6.4 mg.; creatinin, 1 mg.; cholesterol, 278 mg. The blood pressure readings were 205/150; 184/140; 180/150; 164/100, 176/110. He was treated with diet, insulin, chloral hydrate and digitalis. His condition improved and he was again allowed to go home.

He was admitted again on August 28 for the fourth time, with cough, hemoptysis, insomnia, pain in the right upper quadrant, dyspnea and edema of the legs. He had been active since his discharge from the hos-

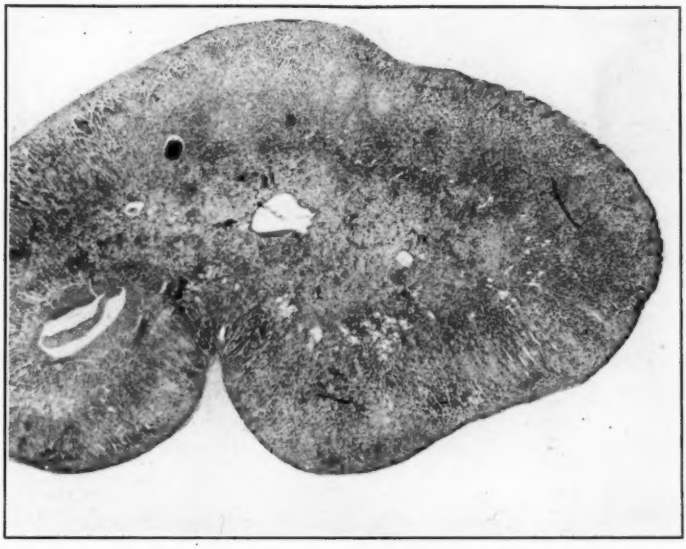

FIG. 3.—Section of adrenal gland (× 7), showing moderate enlargement and beginning hyperplasia.

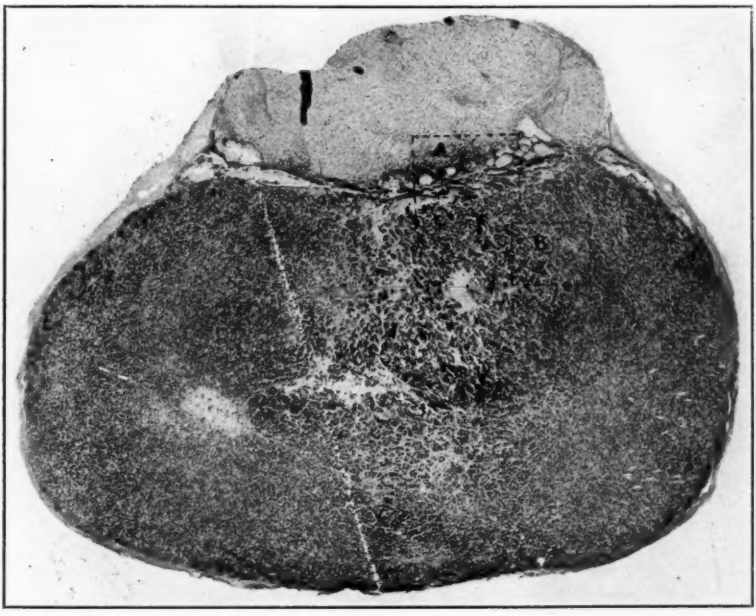

FIG. 4.—Section of hypophysis (× 7), showing hyperplasia of basophil cells, though no actual circumscribed adenoma.

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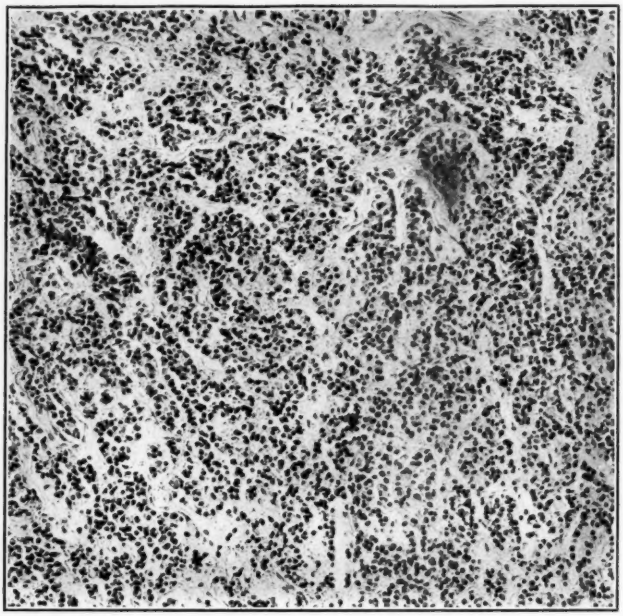

FIG. 5.—Section of anterior lobe (× 150) as indicated on Fig. 4 as *B;* showing hyperplastic cords of basophil cells.

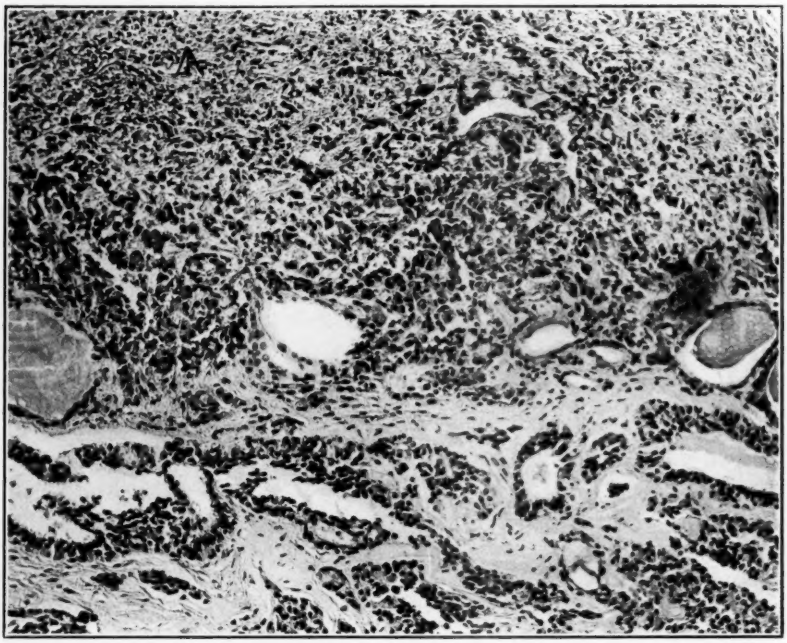

FIG. 6.—Section junction of pars anterior and pars nervosa (× 200) showing invasion by basophil cells into the non-glandular portion.

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pital. Examination showed respiratory distress, cyanosis, flatness in lungs posteriorly, with diminished tactile fremitus and breath sounds, crepitant râles at base, heart enlarged to the left, blood pressure 250/130, pouty abdomen, no fluid, liver 1 inch below the costal margin, and edema of the hands and feet. Roentgen ray of the chest revealed markedly enlarged heart with haziness at base of both lungs. He ran a febrile course—temperature, 102° F.—and rapid pulse, developed pneumonia in the right chest and died.

Autopsy. Lungs: Congestion and edema of the right upper and middle lobes with consolidation of the lower. The left lung presented some pneumonic infiltration in the lower part of the upper and in the lower lobe.

FIG. 7.—Case 2. Abdominal adiposity of hypopituitary type.

The pericardial sac contained 500 cc. of fluid, the surfaces were smooth, the left ventricle was hypertrophied, the valves were competent, there was atheroma in the arch and in the abdominal aorta. The liver extended 8 cm. below the xiphoid cartilage and had a nutmeg mottling appearance throughout. The spleen, pancreas and kidneys showed nothing on gross examination. The adrenals showed a slight diffuse increase in the size of the organ (Fig. 3). The pituitary gland weighed 0.72 gm. It was firm and slightly, though definitely, enlarged (Fig. 4). Section revealed several diffuse elongated whitish areas in the anterior lobe. The sella turcica was normal in contour and the clinoid processes were well preserved. The cellular elements in the pituitary showed a striking predominance of basophils, con-

centrated toward the border between the lobes and a direct invasion of the posterior lobe (Figs. 5 and 6).

Anatomic Diagnosis. Massive bronchopneumonia of both lungs, serous pericarditis, left ventricular hypertrophy, myocardial fibrosis, chronic passive congestion of the lungs, liver and spleen.

CASE 2 (Fig. 7).—J. R., male, aged 37, presented himself at the outpatient department at St. Luke's Hospital in January, 1934, for examination. He had for some years been a donor for blood transfusions and reported that he always felt better after giving blood. He has always been fat and well. He had had bitemporal headaches off and on for some time.

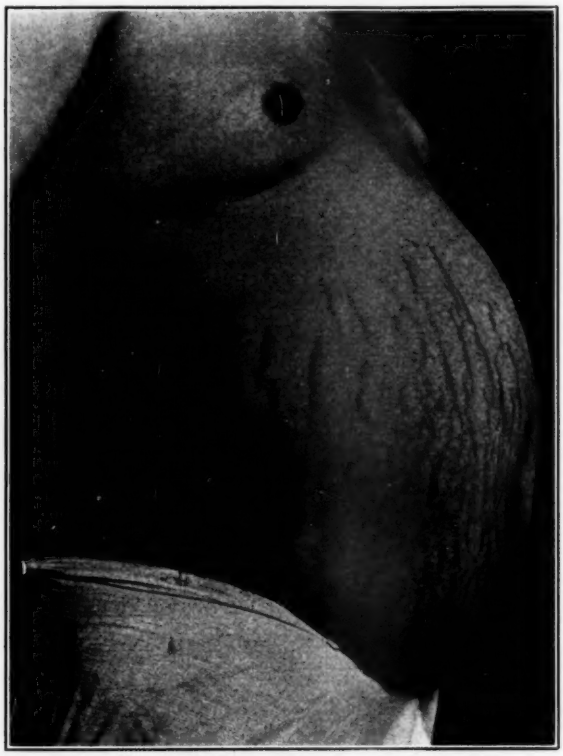

FIG. 8.—Case 2, showing purplish lineæ atrophicæ on abdomen and in axillæ.

Physical examination showed a man of medium height with generalized obesity, but especially marked about the abdomen. Slight exophthalmos was present and there were purplish lineæ atrophicæ on the abdomen (Fig. 8). The genitalia were small. The heart was slightly enlarged. The skin was pale and there was the average amount of body hair. The blood pressure was 170/110. *Laboratory examinations:* Hemoglobin, 101%; red blood cells, 5,450,000; white blood cells, 7100, and neutrophils, 76%. The blood Wassermann test and the urine were negative. The basal metabolic rate was +19%. A Roentgen ray of the skull showed the sella turcica to be of average size and there was no erosion.

This case presents exophthalmos, headaches, obesity, hypertension, purplish abdominal striæ, polycythemia, small genitalia and loss of libido—a group of signs which are characteristic of the basophilic syndrome. The occurrence of the blood changes therein is no doubt a factor in making the patient able to pursue his occupation as a donor.

Discussion. By the finding of basophilic hyperplasia of the pituitary in a patient suffering from hypertension, diabetes and many of the classical signs of pituitary basophilism, it is possible to forge another link in the chain of evidence implicating the hypophysis in certain clinical states associated with hypertension. This patient showed also abdominal adiposity, plethora, polycythemia, purplish lineæ atrophicæ, hypertrichosis, changes in the bony structure suggesting decalcification, exophthalmos, glycosuria and small genitalia and impotence.

This grouping of signs has been associated with a basophilic adenoma of the pituitary and will link up that syndrome with those cases reported by Cushing,[9,10,11] A significant report by Graef, Rottion and Bunim[12] on a case of hypertension, glycosuria, purplish abdominal striæ associated with an adrenal tumor throws some doubt upon the relationship of the pituitary to this syndrome. However, associated changes in both the adrenals and pituitary have been constantly commented upon both in clinical pathologic studies and from the results of animal experimentation. Owing to the dominant position held by the hypophysis as a regulator of activity in the thyroid, adrenals and gonads, it is not presumptuous in the light of our present knowledge to continue to regard the syndrome of pituitary basophilism as a primary pituitary disturbance.

What is the relationship then of this syndrome to hypertension? Cushing has in a larger series of observations tried to demonstrate that hyperactivation of the neurohypophysis by a basophil cell hyperplasia and posterior lobe invasion is the rule in certain types of hypertension. Eclampsia, essential hypertension and the hypertension of the arteriosclerotic are evidently often accompanied by a basophilia, which apparently activates the posterior lobe and increases its humoral output. Just what the hormone secreted from the basophil cells may represent in hypophyseal activity is a point yet to be determined; nor is it yet certain that the sex hormone arises from these cells. A pressor substance from the posterior lobe has long been recognized and the neural connection with the hypothalamic centers is an accepted anatomic and functional fact. On the other hand, a conclusion as to etiology of hypertension in these basophilias is impossible without a consideration of its association with the adrenal glands. The known relationship between these glands and their important vegetative connection must be further understood before evaluation of hypertension can be made.

We are ready to consider that the hypertension of pituitary

basophilism may be associated with either a basophilic adenoma or a basophilic hyperplasia and invasion of these cells into the pars nervosa. A case showing this situation is reported with autopsy, and a second one, still living, is shown with a typical clinical picture. It would seem worth while in the light of these 2 cases to scan carefully our medical clinics for further confirmation of this interesting relationship.

Summary. 1. The clinical syndrome of pituitary basophilism is protean, being reported with basophil adenoma, adrenal adenoma and other unverified cases.

2. One case reported with a hypertensive plethoric syndrome characteristic of pituitary basophilism was found to have a basophil hyperplasia of the hypophysis.

3. A second case with a less marked simulation of the classical syndrome is presented.

4. Additional evidence is offered that hyperplasia of the basophil cells of the anterior pituitary may induce a hypertension and a typical syndrome of pituitary basophilism as well.

5. It behooves us therefore to investigate further the pituitary—adrenal—diencephalic complex as a basic cause for hypertensive states.

I should like to express my indebtedness to Dr. Lewis F. Frissell, Director of Medical B Service of St. Luke's Hospital, New York, for the privilege of reporting these cases from his Wards and Clinic, and to Dr. Liela C. Knox for coöperation in the pathologic study.

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A SYNDROME SIMULATING DIENCEPHALIC STIMULATION OCCURRING IN PATIENTS WITH ESSENTIAL HYPERTENSION.

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The similarity between the reaction in human beings to β-methyl-acetyl-cholin and the reaction to stimulation of diencephalic centers has recently been pointed out by Page.[1] Since observing this reaction, its great similarity to a spontaneous syndrome occurring usua ly in young patients (ages 18 to 29) suffering from essential hypertension has become evident. In the past 2 years 11 such patients have been studied. Following is a description of what was observed to a more or less marked degree in all of the patients:

Attacks arise spontaneously at times, but are usually brought on by excitement. A blush first appears over the forehead and cheeks, spreading down to the neck and trunk. Particularly over the trunk it is blotchy, but often becomes confluent. Over the reddened area tiny beads of perspiration appear. The legs and arms are rarely involved, and the hands, especially the fingers, may be cyanotic and cold. The heart rate increases and the patient may complain of palpitation. The blood pressure rises moderately (20 to 30 mm. Hg). The eyes water, or actual crying occurs. Salivation may take place, and the patients often state that they feel choked. Respiration is less frequent, deeper, often sighing, and may become labored. Movement of the intestine is felt by the patient and often can be heard by an observer.

These signs and symptoms seldom last for more than a few minutes, but may occur a number of times in a day with greatly varying intensity.

The syndrome has been observed in this fully developed form largely in young women. Without exception the disease has been severe, as evidenced by high blood pressure (averaging 220 mm. systolic and 146 mm. Hg diastolic), and in 1 case by a rapidly fatal outcome. Other characteristics were sexual frigidity, profuse menstruation and high-strung temperament. Often tremor of the hands was present, and attacks of general trembling were not uncommon. Slight enlargement of the thyroid gland was often observed; the basal metabolism was either normal or slightly elevated (+5 to +20). Sensitiveness to cold and a complaint either of "dead fingers" or of numbness of the hands on exposure to cold were frequent. Ringing in the ears, nausea, and a feeling of tightness of the scalp over the vertex were common complaints.

While this syndrome was most commonly observed in girls and young women, various components of it have often been seen in older patients. Especially common are perspiration, flushing and palpitation. Older patients whose blood pressure has long been fixed at a high level rarely exhibit it.

The mechanism of the syndrome is unknown, but it has so many features characteristic of stimulation of the centers within the diencephalon that it seems profitable to examine the evidence suggesting its origin at this site in detail.

Neurologists believe that the hypothalamus is the essential instrument of emotional expression. Upon it rests the responsibility for translating into behavior the initiative to action which is taken by the cerebral cortex.[2] It is indeed this part of the brain which organizes, by means of the sympathetic and parasympathetic systems, the most vital activities of the body itself, its visceral functions, its growth and metabolism, and even such appetites as those of sex. More especially, it is in the neopallium (*e. g.*, the non-olfactory cortex) that control of such activities is most highly concentrated. Nervous impulses circulate through the brain to effect coördination between the instruments of the conative dispositions and those of the affective (thalamus) and the cognitive (neopallium) dispositions of the mind. This mechanism involves the hypothalamus, which presumably sets the emotional tone that colors all mental and muscular activity, in particular in artistic expression and self-consciousness.[2]

Experimental proof of the function of the diencephalon in the emotional activation of the sympathetic nervous system has been supplied by the observations of Cannon and Britton,[3] but more especially by Bard.[4,5] They were able to bring about a state which they called "sham rage" in cats by removal of the cerebral hemispheres. Such signs of widespread sympathetic activity were apparent as erection of hair, rapid heart rate, profuse sweating at the toe pads, high arterial pressure and discharge of epinephrin. The disposition to exhibit behavior which is primitively emotional, comparable to that which enables the normal animal to meet critical situations in life, gives strong support to the view that the nervous mechanisms for the expression of rage are subcortical. The influence of the cortex in this reaction may actually decrease rather than increase that exerted by the subcortical mechanisms (Bard). Bard adopts the view, first advanced by Hughlings Jackson and elaborated by Head, that the cortex normally holds in check those activities of the lower and more archaic centers, the unrestrained action of which would seriously interfere with its more discriminative reactions. He regards action of the caudal half of the hypothalamus and the most ventral and most caudal fractions of the corresponding segments of the thalamus as the portions responsible for the exhibition of sham rage. The diencephalic

mechanism is activated during times of stress and emergencies, and is responsible for the widespread nervous discharge which then occurs.

Both sympathetic and parasympathetic centers are believed to exist within the hypothalamus. The anterior group may be "parasympathetic" because of the relationship of the tuberal nuclei to the craniosacral division of the autonomic nervous system with its peripheral control through vagus and pelvic nerves.[7] The posterior groups, in the walls of the posterior portion of the third ventricle above the corpora mammillaria, are said to contain the sympathetic centers.

At lower levels, bulbospinal centers exist which normally suffice for tonic and reflex sympathetic discharges. They can act independently, but may be influenced by centers at a higher level.

Cushing[6] has supplied strong evidence for locating in man the presence of parasympathetic centers in the hypothalamus by injecting various substances into the ventricles. Vasodilatation, sweating, lacrimation, salivation, increased peristalsis and vomiting occurred. A small discrete encapsulated tumor, so placed as to impinge upon the anterior and superior portion of the thalmus on each side, was found in a patient to elicit at first restlessness, then sudden intense dilatation of the vessels of the face, arms and breasts, sudden rise in blood pressure, lacrimation, sweating, salivation, increase in heart rate, retardation of respiratory rate and hiccoughs, ending with transient shivering.[7] Clearly these attacks, which Penfield called "diencephalic autonomic epilepsy" are explosive, undiscriminating discharges which suggest the proximity of a lesion (tumor) both to parasympathetic and sympathetic centers. The promotor area of the cortex may also participate in the genesis of symptoms believed to be characteristic of central autonomic discharge. Irritation caused by the growth of a tumor often results in increased sweating and vasodilatation on the contralateral side of the body.[8]

In the syndrome observed in patients suffering from essential hypertension, a marked resemblance to that due to different causes and described by Cushing, by Penfield and by Page, is apparent (Table 1).

Clinical experience suggests, accordingly, that in essential hypertension there is evidence of diencephalic irritation. Emotional instability akin to sham rage in cats is a regular occurrence. Phenomena are observed in these patients which suggest strongly regression to more archaic emotional patterns. Their similarity to syndromes resulting from diencephalic stimulation lead to the belief that they, too, have their genesis in the diencephalon.

Case Abstracts. Case 1 (No. 9193).—P. S., female, aged 25. The blood pressure was known to have been normal until 1½ years ago. About 14 months ago the patient noticed that she tired very easily, and that she had

frequent severe headaches. She became restless, sleepless, irritable and complained of "spells" during which she had an uncontrollable desire to yawn and cry. Simultaneously her face felt flushed and hot. Her blood pressure was found to be 182/116 mm. Hg; and urea clearance 91.5% of normal. Fundus examination showed very early arteriolar sclerosis with moderate sausage-shaped arteriolar constriction.

TABLE 1.—SYMPTOMS OF DIENCEPHALIC IRRITATION.

	Essential hypertension.	Acetyl-β-methyl-cholin.	Diencephalic epilepsy.	Intraventricular pituitrin.
Probably parasympathetic	Sweating Vasodilatation Lacrimation Salivation Increased peristalsis Slowed respiration Deepened respiration	Sweating Vasodilatation Lacrimation Salivation Increased peristalsis Slowed respiration Deepened respiration Fall in blood pressure	Sweating Vasodilatation Lacrimation Salivation ..... Slowed respiration Deepened respiration	Sweating. Vasodilatation Lacrimation. Salivation. Increased peristalsis. Slowed respiration. Deepened respiration. Slight slowing of heart rate.
Probably sympathetic	Slight rise in blood pressure Increased heart rate Excitement	..... Increased heart rate	Rise in blood pressure Increased heart rate	Slight rise in blood pressure.
Possibly control release	Fits of uncontrollable anger Excessive irritability	.....	Restlessness	

CASE 2 (No. 8990).—I. S., female, aged 23, has been very much worried over a love affair for the past 16 months. During the last year she noted that she tired easily. Because of her irritability and uncontrollable outburst of temper her blood pressure was measured and found to be elevated. She complains of excessive perspiration most of the time, and often has attacks of violent blushing. Lacrimation and salivation usually accompany the blushing. She states that while she realizes that her behavior only makes her condition worse, she is unable to control herself. The blood pressure was found to be 196/116 mm. Hg; urea clearance 69% of normal. The eye grounds appear normal except for slight arteriolar constriction. Basal metabolism, +7.

CASE 3 (No. 9101).—E. J., female, aged 24, has always been a very nervous person. She noticed for the past few years that she perspires and blushes without any apparent cause, and in the past year the blushing attacks have become very troublesome. Simultaneously she has palpitations, a feeling of tightness and uneasiness in the abdomen and is apt to cry. Tinnitus aurium is almost constantly present. About twice a year she has had attacks strongly suggesting epilepsy. Blood pressure was found to be 208/140 mm. Hg; urea clearance 91.5% of normal. The disk of the fundus is hyperemic, the arterioles tortuous and very slightly constricted, the veins are moderately tortuous and dilated.

CASE 4 (No. 8554).—M. G., female, aged 24, 5 years ago noticed attacks of blurred vision, dizziness and profuse perspiration. Always excitable, in the past few years she has become very irritable and restless. She has attacks of "choking" during which she states she has to breathe very deeply, associated often with flushing and crying. Blood pressure, 248/146 mm. Hg; urea clearance, 87.2; basal metabolism, +33. Moderate constriction and early arteriosclerosis of the arterioles in the fundus was observed.

CASE 5 (No. 9278).—A. S., female, aged 24, first noticed 4 years ago that after emotional excitement her face and upper chest became blotchy

and that she had spots before her eyes and was dizzy. Her systolic blood pressure was found to be 130 mm. She became extremely nervous and irritable 7 months ago and exhibited almost all of the signs and symptoms of "diencephalic irritation." Blood pressure was found to be 210/136 mm. Hg.; urea clearance, 80% of normal; basal metabolism, +15. Slight, if any, constriction of the arterioles of the fundus was observed.

CASE 6 (No. 9317).—R. H., female, aged 17, first suffered 3 years ago from attacks of dizziness and headaches which prostrated her. One year ago she decided to become a nun. Physical examination showed her blood pressure to be 160. For 2 or 3 years she has exhibited attacks quite characteristic of "diencephalic irritation." Unquestionably she suffers from emotional instability and conflict. Blood pressure was found to be 174/118 mm. Hg; urea clearance, 108% of normal; basal metabolism, +4. Moderate tortuosity of the retinal arterioles and but slight constriction was observed.

CASE 7 (No. 9306).—B. H., female, aged 32, has been a high strung, emotional person for the past 10 years or more. Irregularity in her sexual activity has caused much difficulty in her life. Vasomotor instability, as shown by mottled blushing of her face and upper chest with palpitations, has been present for many years. The blood pressure was found to be elevated 8 years ago. At present it is 190/120 mm. Hg; urea clearance, 97% of normal; basal metabolism, +21. The eye grounds are normal.

CASE 8 (No. 9339).—A. R., female, aged 25, for the past few years has noticed attacks quite typical of those described as "diencephalic irritation." Two years ago her blood pressure was found to be 140. It has gradually risen to 200 and now varies from 170 to 230 mm. Hg systolic, and 108 to 138 mm. Hg diastolic; urea clearance, 73% of normal; basal metabolism, +11. The eye-ground disks are hyperemic, the arterioles constricted and the veins dilated. There is very slight perivasculitis.

CASE 9 (O.P.D.).—E. C., female, aged 36, has had many emotional conflicts. She has shown evidence of "diencephalic irritation" for the past 3 to 4 years. Two years ago her blood pressure was normal but is now 162/98 mm. Hg. Urine is normal and no pathologic changes are observed in her eye grounds.

Summary. A syndrome has been described which is observed in its fully developed form largely in young women suffering from essential hypertension, but components of which may occur in many cases of essential hypertension. The signs and symptoms so closely resemble those resulting from irritation of sympathetic and parasympathetic centers in the diencephalon, and possibly the promotor area of the cortex, as to suggest that they originate there. Phenomena also occur in these patients which suggest strongly regression to more archaic emotional patterns, possibly having their genesis in the thalamus and hypothalamus.

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THE EFFECT OF ADRENALIN INJECTION ON THE BLOOD OF PATIENTS WITH AND WITHOUT SPLEENS.

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Recent studies on the effect of adrenalin injection on the blood picture have been influenced so much by Barcroft's[1,2,3] work on the physiologic contraction of the spleen that sight has been lost of early literature on this subject. This has been reviewed ably by Kagi,[4] Edmunds and Stone,[5] Lamson[6,7] and recently by Benhamou.[8]

Although certain investigators find no constant changes in the blood response after the injection of adrenalin, in general the literature records leukocytosis and polycythemia. Some authors[9,10] find a characteristic leukocyte formula with lymphocytosis rapidly followed by neutrophilic leukocytosis. The cause of the white blood cell increase has been variously attributed to stimulation of the vegetative nervous system;[11] to a chemotactic reaction;[12,13] to direct stimulation of myeloid and lymphoid tissue;[5] to functional state of lymphoid tissue;[14] to mechanical alteration in the blood stream;[4] to unequal redistribution of cellular elements;[15] and to contraction of the spleen with expulsion of stored cells.[9,16,17]

An increase of red blood cell and hemoglobin concentration following injection of adrenalin also has been observed in animals and man.[6,16,17,18] Its cause is debated. Earlier workers have ascribed the effect to hemoconcentration. Lamson,[6] for example, believes it is due to constriction of the hepatic veins with loss of plasma. More recent publications[16,19] imply an outpouring of cells from the spleen, despite the fact that increases of blood volume were not obtained.

It is beyond the scope of this paper to evaluate the exact nature of the adrenalin effect on the blood picture. It does, however, seem timely to determine whether or not this drug acts by squeezing from the spleen a reserve supply of blood. Studies with this objective have been made previously by Frey[20] and Edmunds and Stone[5] on animals. In rabbits Frey found the characteristic leukocytosis wanting after splenectomy. In guinea pigs extirpation of the spleen made no difference in the response. Edmunds and Stone found that an increase of white cells, red cells and hemoglobin occurred after adrenalin injection in dogs whether the spleens were intact or removed.

Since observations on animals may be misleading when compared with responses observed in man, it is pertinent to review previous clinical studies where a comparison has been made between patients with and without spleens present. Kreuter[21] and Frey[20] each reported a case in which leukocytosis occurred following adrenalin injection in a splenectomized patient. Schenk[22] did studies on patients with splenomegaly and on 3 patients after splenectomy. Following the subcutaneous injection of 1 to 2 mg. adrenalin there occurred a rise of red blood cells, hemoglobin and white blood cells in all instances.

Yang[17] did a similar study on 3 normals, 4 patients with splenomegaly and on 2 splenectomized patients. There occurred an average increase of about 400,000 red blood cells and 4% hemoglobin in patients with splenomegaly after subcutaneous injection of 0.5 to 1 cc. of 1 to 1000 adrenalin hydrochlorid. No significant alteration in red blood cell or hemoglobin concentration of the normal and splenectomized patients took place. With this moderate gain in red blood cells and hemoglobin, it is not remarkable that subsequent blood volume studies[19] showed no appreciable change. This failure was attributed to a CO method which was believed to record falsely elevated initial values because of absorption of the gas by the spleen.

Recently Benhamou[8] reported results of studies similar to those of Yang. A moderate transitory increase of red blood cells and platelets occurred except in the splenectomized patients. This difference was attributed to the absence of the spleen in the latter cases. However, persistent leukocytosis was observed in all instances, and he therefore concluded that the white blood cell increase was not a function of splenic contraction.

Because of the diverse results and the difficulty in the interpretation of the blood changes produced by adrenalin injection, we felt there was need of determining whether or not the spleen actually was significantly involved in the reaction.

Methods. Blood studies were, therefore, made before and after the subcutaneous injection of adrenalin on 2 normal persons, on 9 patients with

chronic hemolytic jaundice—5 with spleens and 4 without spleens—and on 6 patients with splenomegaly associated with various other diseases.

In each patient a single subcutaneous injection of adrenalin hydrochlorid, 1 to 1000 dilution (Parke-Davis), in doses of 0.8 to 1 cc. was made. The patients experienced characteristic reactions with tachycardia, elevated blood pressure, palpitation, sweating, nervousness and tremor.

Three venous blood samples were obtained in each case, using 0.05 cc. of 20% potassium oxalate as an anticoagulant for 5 cc. of blood. The first sample was taken just before the adrenalin injection; the second, 15 minutes after the injection; the third, several hours later. Capillary blood samples were taken at the same time as the venous blood and an additional capillary sample was taken at 5 minutes after the adrenalin injection. The 5-minute and 15-minute observations were made because the marked effects described by other workers have occurred during the first 15 minutes. The times for the final sample were varied in the hope of finding the optimal time for observing a delayed response.

Red blood cells were enumerated by averaging the counts in two chambers. Hemoglobin was determined in duplicate, using a Sahli hemometer so calibrated that 100% corresponded to an oxygen capacity of 21 volumes of oxygen per cent. This was assumed to be the oxygen capacity of 15.6 gm. of hemoglobin. Hematocrit studies were done and indices determined according to the Wintrobe method.[23] Total white blood cell and platelet counts were made from capillary blood from the ear lobe as well as differential white blood cell counts of 200 cells and determinations of the percentage of reticulocytes in 1000 red blood cells.

Results. The blood studies on 2 normal persons and on 4 splenectomized patients with hemolytic jaundice are recorded in Table 1. The red blood cell and hemoglobin concentrations are seen to have fluctuated no more than may be expected to arise from technical error. Detailed hematocrit indices also were determined, but the changes observed were very small and were regarded as insignificant. Increases of white blood cells, however, appeared to be constant and prolonged. This increase involved neutrophils, lymphocytes and monocytes. For the cases of hemolytic jaundice with spleens, the average white cell counts and the average absolute counts of the different white cells are plotted in Chart I. Young neutrophils showed an immediate decrease and later a return up to and exceeding the initial levels. For the most part these remained within the normal range of 2% to 5%. Reticulocytes in both absolute and percentage numbers were essentially unchanged following the injection of adrenalin. In 3 cases of this group there was a moderate increase in the number of blood platelets after adrenalin injection.

In Table 2 a similar tabulation is made for observations on 5 patients with hemolytic jaundice and splenomegaly. In 2 of these patients (Cases 1 and 5) there occurred a definite but merely transitory increase in red blood cell and hemoglobin concentration. An increase of total white blood cells, involving neutrophils, lymphocytes and monocytes, took place in every instance after adrenalin injection. Here, too, as in Table 1, there was a tendency for young neutrophils to decrease and later to increase in number, but never exceeding in per cent the normal range of such cells. No sig-

nificant change in number of reticulocytes occurred. The average total white cell counts of this group are plotted in Chart I as well as the average absolute counts for the different kinds of white blood cells.

TABLE 1.—OBSERVATIONS ON THE BLOOD PICTURE BEFORE AND AFTER SUBCUTANEOUS INJECTION OF ADRENALIN HYDROCHLORID, 0.8 TO 1 CC., IN 2 NORMAL SUBJECTS AND 4 SPLENECTOMIZED PATIENTS WITH CHRONIC HEMOLYTIC JAUNDICE.

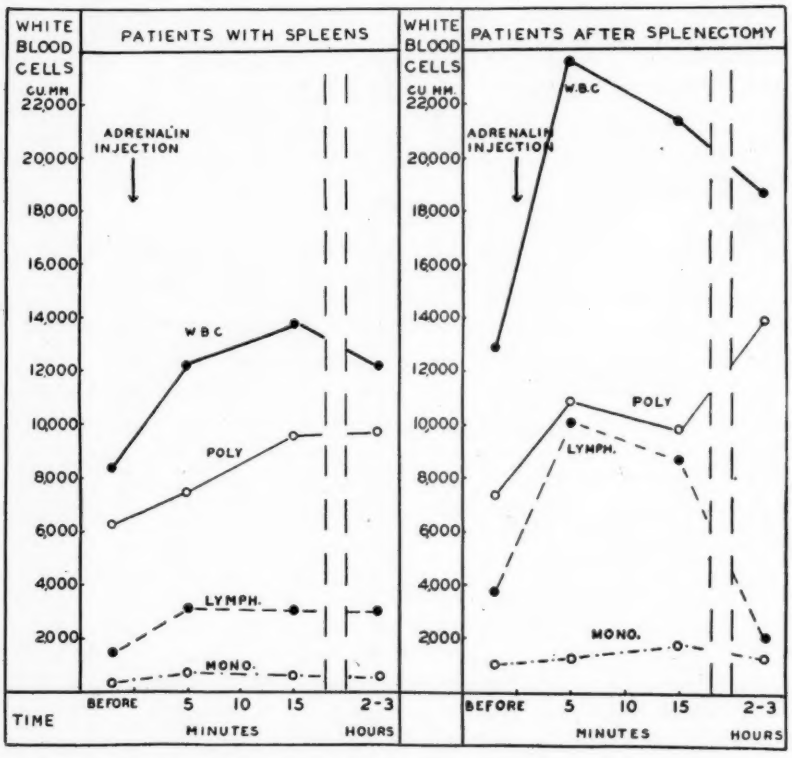
Case.	Time.	Red cells, millions per c.mm.	Hemoglobin, gm. per 100 cc.	Hematocrit, per cent.	Platelets, thousands per c.mm.	White cells, per c.mm.	Neutrophils, per c.mm.	Lymphocytes, per c.mm.	Monocytes, per c.mm.	Young neutrophils, per c.mm.	Young neutrophils, per cent.	Reticulocytes, per cent.
						Normals.						
1 . .	Before	4.88	14.5	42.0	..	9,700	5,820	3,004	436	183	1.9	
	5 min.	..	..	..	..	7,850	5,102	1,884	588	76	1.0	
	15 min.	4.87	14.4	42.3	..	9,450	6,284	2,268	614	125	1.3	
	4½ hrs.	4.88	14.7	43.8	..	10,700	7,222	2,407	856	289	2.7	
2 . .	Before	4.96	14.8	42.7	..	7,400	3,737	2,300	888	150	2.0	0.8
	5 min.	..	..	..	..	10,600	4,823	4,300	1000	320	3.0	0.6
	15 min.	4.97	14.8	43.0	..	12,300	6,396	3,870	1600	126	1.0	0.8
	1 hr.	5.09	14.6	42.7	..	10,600	5,883	3,000	800	270	2.5	1.0
	3½ hrs.	4.90	14.8	43.2	..	12,600	8,820	1,950	1260	380	3.0	0.6
						4 Splenectomized Patients With Chronic Hemolytic Jaundice.						
1 . .	Before	5.55	18.8	52.4	402	8,800	4,400	2,500	1100	89	1.0	0.6
	5 min.	..	..	..	364	16,950	5,560	9,237	1186	83	0.5	0.4
	15 min.	5.55	18.7	50.9	467	17,900	6,470	7,876	2236	65	0.4	0.2
	4 hrs.	5.64	18.8	48.8	389	14,425	7,600	2,957	1658	315	2.2	0.3
2 . .	Before	5.92	17.5	49.1	..	16,000	8,560	5,280	1520	86	0.5	1.0
	5 min.	..	..	..	..	32,000	14,700	14,080	1600	300	0.9	1.8
	15 min.	5.95	17.3	48.5	..	30,600	13.800	11,484	3521	139	0.5	1.4
	4 hrs.	6.04	17.3	46.3	..	22,200	17,840	1,554	1110	457	2.0	1.7
3 . .	Before	4.69	13.6	38.2	366	9,350	5,300	3,179	467	92	0.5	1.1
	5 min.	..	..	..	468	22,000	12,440	7,810	1100	375	1.7	0.6
	15 min.	4.46	13.4	37.8	..	15,500	7,480	7,595	232	209	1.3	1.0
	3½ hrs.	4.02	12.0	36.6	428	17,850	14,300	1,785	1071	641	3.5	0.9
4 . .	Before	4.43	14.0	42.6	828	17,470	11,181	4,455	1136	437	2.5	1.3
	15 min.	..	..	..	1002	21,250	11,582	7,969	1275	212	1.0	1.2
	1 hr.	4.50	14.0	41.4	1030	26,780	17,942	6,829	1740	133	0.5	2.2
	2 hrs.	4.37	14.0	41.6	950	20,300	16,139	2,030	1522	406	2.0	1.9

NOTE.—Counts of basophils and eosinophils were not tabulated because their numbers were not regarded as significantly altered.

In Table 3 a similar series of observations is recorded for patients with splenomegaly associated with various diseases. Cases 1 to 4, inclusive, had chronic myeloid leukemia; Case 5 had osteosclerotic anemia and Case 6, polycythemia vera. Although the data are not so complete as in the other groups, one can observe that no appreciable change occurred in red blood count or hemoglobin except in Case 1, where a moderate rise took place; that an increase of white blood cells likewise was the rule. Under the heading "young neutro-

phils" are included myelocytes and myeloblasts. In several cases these appear to be increased in absolute and percentage numbers after the injection of adrenalin. However, the white cell distribution in leukemia is notoriously unstable and the changes observed may not be interpreted strictly as part of a causative sequence.

CHART I.—Illustrating changes in the absolute number of white blood cells before and after the subcutaneous injection of adrenalin in patients with chronic hemolytic jaundice.



Although absolute white blood cell changes appeared to be more labile after splenectomy than when spleens were intact, the percentage increase was not very different in the two groups of cases.

Discussion. It is obvious from the data presented that little difference was noted in the effect of adrenalin upon the peripheral blood values in hemolytic jaundice in patients with or without spleens. The fact that similar results were obtained in a miscellaneous group with splenomegaly indicates that the lack of difference is not due to a peculiarity of the disease, hemolytic jaundice. Moreover, this disease should be ideal for demonstrating a change in the blood picture following adrenalin injection, since it is charac-

terized by marked congestion and cellularity of the splenic pulp with little fibrosis or thickening of the capsule.

TABLE 2.—OBSERVATIONS ON THE BLOOD PICTURE BEFORE AND AFTER SUBCUTANEOUS INJECTION OF ADRENALIN HYDROCHLORID, 0.8 TO 1 CC., IN 5 PATIENTS WITH CHRONIC HEMOLYTIC JAUNDICE.

Case.	Time.	Red cells, millions per c.mm.	Hemoglobin, gm. per 100 cc.	Hematocrit, per cent.	Platelets, thousands per c.mm.	White cells, per c.mm.	Neutrophils, per c.mm.	Lymphocytes, per c.mm.	Monocytes, per c.mm.	Young neutrophils, per c.mm.	Young neutrophils, per cent.	Reticulocytes, per cent.
1 . .	Before	3.13	7.8	22.1	201	4,700	3,220	794	324	187	4.0	14.3
	5 min.	..	..	..	249	18,600	10,825	5300	1950	335	1.8	20.3
	15 min.	3.88	10.5	32.8	243	19,000	10,835	6460	855	165	0.8	15.0
	3½ hrs.	3.03	7.9	21.6	200	9,450	7,350	945	519	403	4.2	19.2
2 . .	Before	4.70	15.6	48.7	..	7,650	5,840	1262	228	88	1.1	1.1
	5 min.	..	..	..	..	7,950	6,045	1431	198	155	1.9	0.7
	15 min.	4.84	15.5	47.2	..	8,350	6,370	1419	374	130	1.6	0.6
	2 hrs.	4.98	15.1	44.1	..	10,700	9,350	1070	214	50	4.7	0.7
3 . .	Before	4.04	14.5	41.7	..	10,420	8,320	1146	677	169	1.6	2.8
	5 min.	..	..	..	..	12,800	8,750	3136	256	88	0.7	
	15 min.	3.96	14.7	43.8	..	15,900	11,600	2862	397	315	2.0	2.7
	3½ hrs.	3.97	15.0	41.0	..	13,770	9,900	2134	1032	523	3.7	3.0
4 . .	Before	5.21	16.7	46.5	..	11,200	7,190	2970	336	146	1.3	0.7
	5 min.	..	..	..	..	8,350	4,620	2840	542	94	1.3	1.2
	15 min.	5.11	16.6	45.8	..	13,250	9,300	2580	1060	188	1.4	0.8
	3 hrs.	4.91	15.7	46.0	..	14,800	11,600	1480	962	610	4.1	1.0
5 . .	Before	3.53	12.4	32.8	214	8,300	6,515	1369	124	290	3.5	11.6
	5 min.	..	..	..	210	13,600	..	..	..	..	..	10.8
	15 min.	4.32	13.3	37.3	373	12,700	10,247	1778	317	254	2.0	11.4
	1 hr.	4.80	13.7	36.6	280	15,900	12,322	2600	477	397	2.5	12.0
	2 hrs.	3.67	12.3	35.0	..	12,100	10,466	1028	60	665	5.5	6.8

In spite of the fact that the doses used and the time of observations compare closely with the methods of Yang, Benhamou and others, who found red blood cell and hemoglobin increases, we failed to get constant or persistent changes in these constituents. Granted that the time of observations may have caused the response described by some authors to be missed, nevertheless such a transitory change could have little physiologic significance. In the normal dog, splenic contracture is said to increase the circulating blood volume by one-fifth.[1] If a comparable effect is produced in normal man, how much greater then should be the effect in cases with splenomegaly.

Admittedly our studies should have included blood volume determinations. The changes we observed were so trifling in the case of red blood cell and hemoglobin concentrations that we did not think at the time that blood volume determinations were essential. If we had injected larger doses of adrenalin, as Edmunds and Stone did with dogs, we might have found more pronounced effects.

In all types of patients studied there occurred a sharp leukocytosis, involving both myeloid and lymphoid cells, which subsided after

several hours. Certainly, since splenectomized patients exhibit the phenomenon as readily as those with spleens intact, this change is not a splenic function alone.

TABLE 3.—OBSERVATIONS ON THE BLOOD PICTURE BEFORE AND AFTER SUBCUTANEOUS INJECTION OF ADRENALIN HYDROCHLORID, 0.8 TO 1 CC., IN 6 PATIENTS WITH SPLENOMEGALY.

Case.	Time.	Red cells, millions per c.mm.	Hemoglobin, gm. per 100 cc.	Hematocrit, per cent.	White cells, per c.mm.	Neutrophils, per c.mm.	Lymphocytes, per c.mm.	Monocytes, per c.mm.	Young neutrophils, per c.mm.	Young neutrophils, per cent.	Reticulocytes, per cent.
Chronic Myelogenous Leukemia.											
1	Before	4.32	15.0	44.0	4,600	2,944	841	335	300	6.5	0.6
	5 min.	..	..	..	5,900	3,097	1197	826	177	3.0	1.2
	15 min.	4.90	15.6	48.6	8,500	4,430	2556	724	85	1.0	1.0
	1 hr.	4.41	14.8	44.9	4,500	2,610	877	472	315	7.0	1.8
	3½ hrs.	4.07	14.0	44.0	4,850	3,273	630	606	339	7.0	1.4
2	Before	3.81	12.5	34.9	184,000	69,900	2760	..	107,640	58.5	
	5 min.	..	..	..	261,000	104,400	7830	1300	138,310	53.0	
	15 min.	3.90	11.7	35.2	261,000	95,265	3915	7800	147,465	56.5	
	4 hrs.	3.65	11.4	34.2	150,000	60,000	1500	..	85,500	57.0	
3	Before	4.62	15.6	..	37,000	31,968	370	1110	2,220	6.0	2.8
	15 min.	5.20	16.2	..	92,000	68,490	4440	1380	8,740	9.5	3.2
4	Before	4.13	11.8	..	13,300	7,780	1200	1900	665	5.0	8.0
	15 min.	4.44	12.0	..	31,000	15,650	2170	4184	2,790	9.0	8.4
Osteosclerotic Anemia.											
5	Before	2.43	6.7	..	4,150	1,743	1162	664	414	10.0	4.0
	15 min.	2.63	7.6	..	19,200	4,416	9792	2688	2,112	11.0	8.2
	2 hrs.	2.30	6.7	..	5,050	2,525	1161	252	807	16.0	5.7
	5 hrs.	2.20	6.9	..	4,750	..	..	..	..	..	3.8
Polycythemia Rubra Vera.											
6	Before	7.28	19.3	..	15,200	12,060	1444	836	..	..	1.9
	15 min.	7.62	19.0	..	20,400	17,240	1938	816	..	..	2.2

No significant increase of either young white cells or of young red cells was observed. If the germinal centers, such as occur in the bone marrow, spleen and lymph nodes, were involved in the blood changes, one would expect an ejection predominantly of these young forms. This did not occur, except in certain cases of the miscellaneous group where immature cells already existed. In these instances the ratio of mature to immature forms was probably not significantly altered by the injection of adrenalin.

It is not implied that adrenalin or other drugs do not cause splenic contraction, for they most assuredly do; nor is it denied that the spleen may function as a reservoir for the circulating blood, as suggested by Barcroft. It is believed, however, because of a critical review of previous studies, particularly those of Schenk[22] and

Benhamou,[8] as well as our own, that the adrenalin test, as applied to cases with pathologically enlarged spleens, is not a measure of splenic function alone.

The red blood cell changes observed by other investigators and in 3 of our cases may be due to an outpouring from the spleen as a blood reservoir, but one should recall that there are other depots for the circulating blood—such as the liver, skin and splanchnic vessels, which are also susceptible to adrenalin stimulation. More likely an increase of red blood cells and hemoglobin without corresponding increase of blood volume would be the result of hemoconcentration. The white blood cell increase we also prefer to explain as due to a mechanical alteration in the blood stream, a theory propounded by Kagi.[4] These cells, either pooled in inactive vascular beds or lying along the periphery of the vessel walls may be thrust into the axial blood stream by active contraction of the blood-vessels or by increased velocity of the axial flow.

Summary and Conclusions. 1. Blood studies before and after the subcutaneous injection of adrenalin were made on 2 normal subjects, on 9 patients with hemolytic jaundice—5 with splenomegaly and 4 with their spleens removed—and on 5 patients with splenomegaly from miscellaneous diseases.

2. In no case was there a significantly sustained change of concentration of the red blood cells, of hematocrit or of hemoglobin. In all cases leukocytosis involving both myeloid and lymphoid cells occurred. This increase in cells was characterized by mature forms.

3. Since the changes observed were not greater in patients with spleens than in those after splenectomy, they appear not to be due to splenic contraction.

4. It is suggested that a mechanical alteration in the blood stream involving many areas and organs in the body is responsible for the effects observed.

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EXTREME TACHYCARDIA IN THE NEWBORN.

With Report of a Case.

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Reports of cases of very rapid heart rates in infants have come from many sources and are not as infrequent as might be supposed. The use of the electrocardiograph has, of course, made it much easier to recognize and classify the disorder and has undoubtedly given impetus to the more frequent submission of reports. No attempt will be made here to review the literature exhaustively since this has been done in several published papers. Those bearing on the points of special interest will be mentioned.

The youngest case on record is that of Werley[17] whose patient

was 4 days old when the condition was recognized. The rate as determined by polygraph was 307 and the child was intensely cyanotic. Death occurred on the 6th day and necropsy failed to reveal any significant cardiac lesions.

Electrocardiographic tracings were obtained in Colgate and McCulloch's[3] 2 patients in whom the age at onset of the tachycardia was 21 and 24 days, respectively. The rate in the former was 250 and the latter 291. Both patients were free of symptoms at the time of the report, the first infant having gone 6 months and the second 7 without a recognized attack. No etiology was discovered.

Doxiades[5] reported the case of a newborn the onset of whose first attack came at the age of 7 days and who had in all 4 episodes of tachycardia, each lasting several days except the last which terminated in 24 hours. The electrocardiogram showed auricular tachycardia. There were no subsequent attacks during 4 months of observation.

In 2 cases cited by von Bernuth,[15] 1 of an infant of 3 weeks and the other of an infant of 2 months, the attacks of tachycardia came on suddenly and were associated with pronounced cyanosis and symptoms resembling shock. In the younger infant improvement after the first attack was followed by recurrence and death. The course in the older child showed no remission. Necropsy revealed in both cases diffuse encephalitis which the author believed was the etiologic factor. In an earlier paper[14] the same author offered 3 cases suggesting widely differing possible etiologies. One of his patients had paroxysmal tachycardia following a toxic myocarditis complicating chorea. A second had attacks "induced by worry" and a third was ill with progressive muscular dystrophy with which the seizures of tachycardia were thought to be associated.

DeBruin's[4] patient was 5 weeks old and the tachycardia, rate 280, was thought to be due to encephalitis. The patient recovered.

A case of tachycardia associated with congenital heart disease was observed by Schuster and Patterson.[10] Cyanosis and dyspnea had been present from birth but the child was first seen at the age of 2 months. It lived only 2 days longer and had many paroxysms with uncountable pulse, while the interval rate was 180 to 200. Necropsy showed transposition of the great vessels and several anomalous communications between the cardiac chambers.

O'Flyn[9] presents the case of a child aged 8 months who had two attacks of tachycardia without forewarning, lasting 8 days and 24 hours respectively, and during which the only untoward symptom was anorexia, cyanosis being absent. The cardiac rate during the attacks could not be determined but an electrocardiogram taken after the termination of the second attack showed no abnormalities. Small doses of digitalis had no effect.

Koplik[7] reported 3 cases: one associated with bronchitis at the onset had repeated paroxysms for two years; another, with a rate

of 240 when seen at the age of 3 years, had had attacks since the age of 6 months, but had never been acutely ill. The writer found digitalis of value in controlling the acute episode but not in preventing its occurrence.

Malossi's[8] paper contains electrocardiographic tracings illustrating both the onset and the end of a paroxysm. The rate in 1 case, a child aged 6 years, was 240 and in the other, an infant aged 1 year ill with pertussis, was 260. The tracings suggest flutter rather than tachycardia. The child with pertussis had no recurrence of tachycardia after recovery.

The influence of congenital lues as an etiologic factor is discussed by Franke and Weiner[6] of whose 2 patients one, a boy aged 10, had a positive Wassermann reaction. The other, a girl aged 11, had, as a complication of the tachycardia, ischemic gangrene of both legs for which amputation was necessary. The ischemia was thought to be due to an embolus in the lower aorta which had arisen either from stagnant blood in the auricles (as is seen in auricular fibrillation) or from coexistent vegetative endocarditis.

Willius and Amberg[18] found difficulty in distinguishing between simple tachycardia and auricular flutter in the individual case. Subsequently they[19] reviewed many of the known cases and discussed the criteria for classifying the disorder.

Of 4 cases studied by Shookhoff, Litvak and Matusoff,[12] 3 were thought to be flutter with one to one rhythm. One patient had only two attacks and showed no other findings. Another had the first attack of tachycardia while convalescent from pertussis but has continued to have them since, uninfluenced by medication. The third and fourth cases were associated with myocarditis and congestive failure. Necropsy findings in the last case, presented in detail, show round-cell infiltration, considered a healing infectious myocarditis.

Brown[1] reviews and analyzes a number of cases and reports that of a $3\frac{1}{2}$-year-old child who had had paroxysms every 3 to 4 days from the first year of life. The rate was about 200 and there were no subjective symptoms.

A rhabdomyoma involving the conduction system was found at necropsy on a 10-month-old girl observed by Wegman and Egbert.[16] The patient had had symptoms for several months but the cardiac arrhythmia, believed to be auricular flutter, was noted only on the day of death.

Tatafiore[13] does not add any new cases but describes the physiologic and pathologic modifications of the heart rate in children.

In 1931 Carr and McClure[2] described the case of a newborn infant whose apex rate at birth was 180. At the age of 26 hours an electrocardiogram showed auricular flutter. By the tenth day of life the cardiac rhythm was normal and no further abnormalities were noted.

Recently Sherman and Schless[11] have recorded the case of a child who was known to have a very high fetal heart rate—about 190, but seemed all right at birth. At the age of 1 month, because of breathing difficulties, roentgenograms of the chest were taken which showed enlargement of the cardiac silhouette. An electrocardiogram at the same time showed auricular flutter with 2:1 block—an auricular rate of 464 and a ventricular rate of 232. At the age of 2 months, because of spells of pallor and weakness, she was admitted to the hospital where similar findings were made. The baby was treated with digitalis and normal rhythm was established and has continued since. They ascribed the disorder to immaturity of the conduction bundle.

The following case is reported as another illustration of benign cardiac arrhythmia in the newborn, where no etiology is apparent.

Case Report. J. C., white male, born May 17, 1933, was admitted to the Pediatric Service of the New Haven Hospital on June 10, 1933, at the age of 24 days, referred by Dr. W. C. McGuire. The chief complaint was heavy breathing and loss of appetite.

The family history was non-contributory; the father aged 33, the mother, 27, and 1 female sibling, 3, were in good health.

The pregnancy had not been abnormal and the delivery was spontaneous, having taken place in a hospital after a labor of 90 minutes. The fetal heart rate varied between 140 and 160. Birth weight was 8 pounds, 2 ounces, and physical examination was reported as negative. At the age of 9 days, when the patient and mother were discharged, he weighed 7 pounds 12 ounces. Breast feedings alone were given.

Nothing untoward was noticed until 5 days before admission when the child began to have 4 or 5 loose stools daily. Beginning at 2 A.M. on the day before admission the baby refused most of his feedings, was breathing heavily and looked ill. The mother noticed that the urine colored the diaper pink. He was given a teaspoonful of milk of magnesia. On the day of admission the patient had a very green stool. A physician who was called ordered a soda enema. However, the child seemed to be growing weaker and the dyspnea more marked so Dr. McGuire was called in consultation. He detected an extremely rapid heart rate and sent the child to the hospital.

The patient was admitted to the accident room at 8 P.M.; at this time his temperature was 36.8° C., and respirations 76 per minute. He was well developed and nourished but was pale and looked gravely ill. The lips were slightly cyanotic and the respirations shallow although the child was crying shrilly. The heart, which did not seem enlarged, was beating with regular rhythm at a rate too rapid to be counted but estimated at 300 per minute. The breath sounds had a prolonged expiratory phase but there were no râles. The liver was definitely enlarged with the edge 3 fingerbreadths below the costal margin and the spleen was down 1½ fingerbreadths. No peripheral edema could be made out.

Laboratory Data: The red blood cell count was not abnormal. The white blood cell count was 24,000 with 34% neutrophils and 64% lymphocytes. The Kahn test, intradermal tuberculin reaction and urinalysis were all negative.

The child was placed in an oxygen tent and his color improved. Pressure on the eyes, vagi, and the abdomen had no effect on the heart rate. At 2 A.M. he was given an hypodermoclysis of 35 cc. saline and 35 cc. 5% glucose solution. At 2.45 A.M. the child was given morphin, gr. $\frac{1}{100}$ and

digifolin, 0.8 cc., equivalent to 0.08 gm. digitalis. No change was observed in the heart within the next hour.

At 10 A.M. the next morning the child looked much better. His temperature was 37.6° C. The heart rate had decreased to 122 per minute and the respirations to 46. The liver had receded to 2 fingerbreadths below the costal margin. A cardiologist, Dr. H. M. Marvin, reported a third heart sound to be present. An attempt to take an electrocardiogram was unsuccessful because of the baby's muscular movements.

The further course was uneventful and the patient gained 225 gm. during his 12-day stay.

Roentgenograms taken on admission show greatly increased hilar markings and similarly increased peripheral markings extending well out into both lung fields. There is no evidence of infiltration or effusion. Films taken the next day, shortly after reëstablishment of the normal cardiac rate, show a still greater increase in the markings described above. Further films taken 2 and 10 days later show striking and progressive improvement, the last presenting an essentially normal appearance. In view of the clinical picture the roentgenographic findings are compatible with a diagnosis of passive congestion.

For 3 days at home the child did well but on June 25, 15 days after the first admission, the mother noted rapid respirations and by direct auscultation discerned tachycardia. Pallor but not cyanosis was present. When improvement did not appear in 24 hours the child was brought to the hospital.

SECOND ADMISSION. (Patient 39 days old). The temperature was 37.2° C. and respirations 96 per minute. The heart rate was again too rapid to be counted. The lungs were clear but the liver was enlarged as previously.

An electrocardiogram taken on admission shows a rate of 300 with regular rhythm. The deflections are predominantly downward in Lead I and upward in Lead III—left axis deviation (new terminology). There is a tendency to rhythmic alternation in the size of the *T* wave in Lead I. The configuration is compatible with a diagnosis of either auricular tachycardia or auricular flutter with one to one rhythm (Fig. 1).

Roentgenograms were similar to the first ones taken on the previous admission in showing bilaterally increased pulmonary markings.

Forty-five minutes after admission the infant received 0.08 gm. of digitalis as digifolin subcutaneously along with morphin, gr. $\frac{1}{100}$. Six hours later the child seemed better although still pale; the heart rate was about 120 per minute; respirations 50. Another electrocardiogram at this time showed an essentially normal configuration (Fig. 2).

For the remainder of the 7-day stay in the hospital the heart rate varied from 100 to 130 and nothing unusual occurred. He was discharged July 3, having gained no weight.

Again the baby did well at home but 8 days after discharge he lost his appetite and the mother noted tachycardia. There was neither pallor nor cyanosis. Dr. McGuire was called and gave the patient 2 drops of tincture of digitalis every 4 hours. He received, in all, the equivalent of 75 mg. of digitalis without improvement and admission was advised.

THIRD ADMISSION. (Patient 55 days old). Did not look very ill but was slightly cyanotic. Another electrocardiogram was similar to the first (Fig. 3), but showed more persistent alternation in the size of the *T* wave in all leads. Digitalis, 25 mg., in the form of digifolin, was given immediately and 7 hours later. No change was observed until the next morning when the rate was 120 per minute. Cyanosis was no longer present but the liver was still enlarged. The total amount of digitalis was 125 mg.

Two days later the patient was discharged with the heart rate 120 and the liver again at its average size.

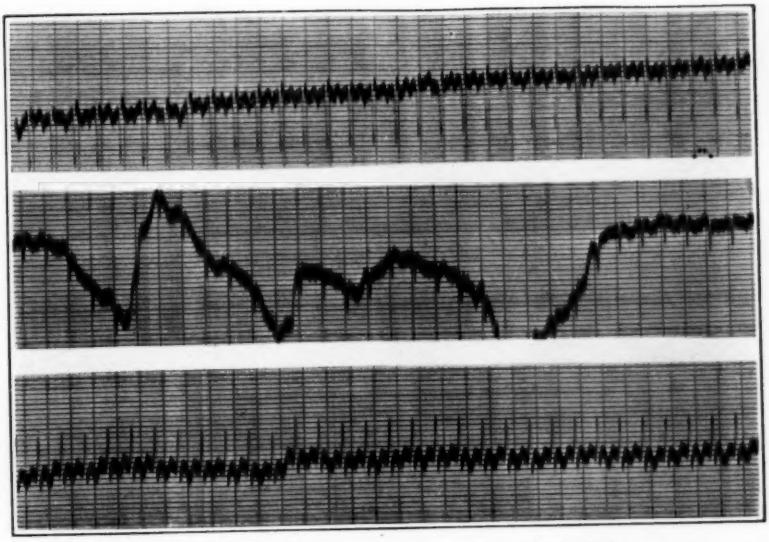

FIG. 1.—Electrocardiogram taken on second admission.

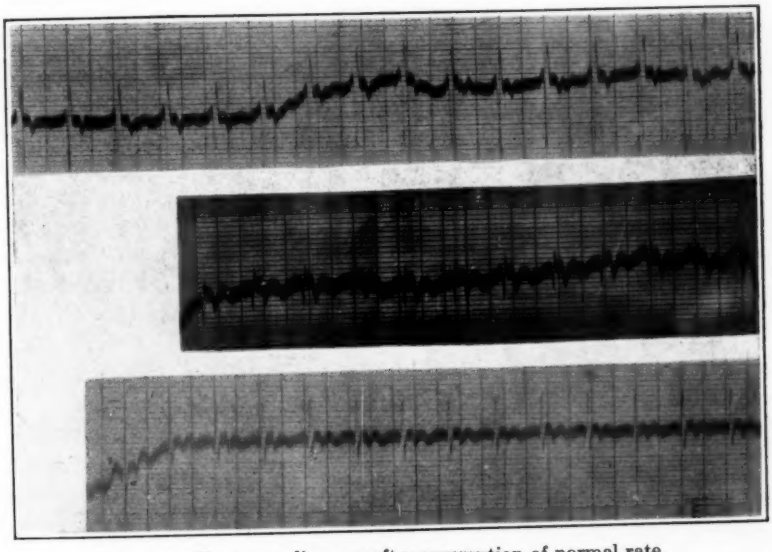

FIG. 2.—Electrocardiogram after resumption of normal rate.

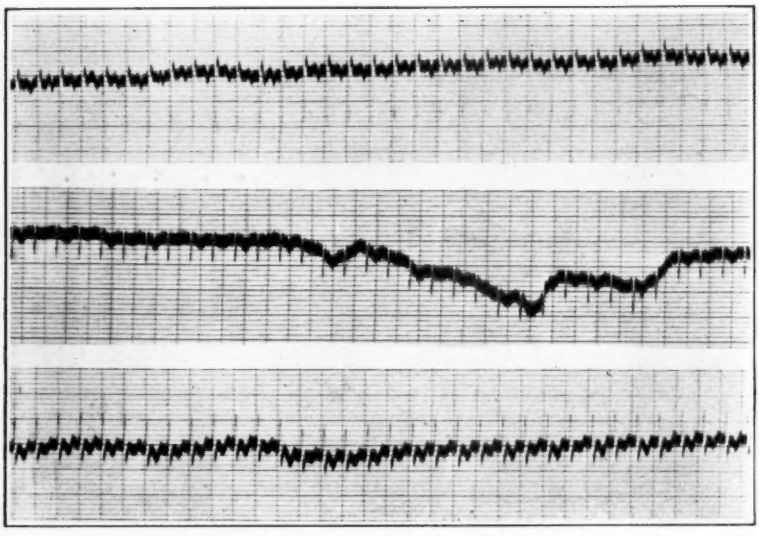

FIG. 3.—Electrocardiogram taken on third admission.

There were no subsequent attacks at home until 3 months after discharge (age 5 months) when the baby became cyanotic during his bath. Although nothing abnormal in the heart was found by the physician the next day the infant was given tincture of digitalis 2 minims 3 times a day for 10 days. About a month and a half after this there was another seizure of tachycardia lasting 3 hours. Two months following this the baby had a very transient paroxysm. Since then he has been free of attacks, has gained weight and developed in a normal fashion.

Discussion. This case presents several unusual aspects. The observations on the fetal heart rate offered an opportunity to detect abnormalities of rate at a time when the latter tends to be high naturally. No such changes were encountered.

Careful observation of the child has failed to give any hint as to what the etiology might be and the decreased frequency and lessened severity of the attacks makes it doubtful if any light will be thrown on this point. The favorable course thus far is compatible with a good prognosis and whatever factors produced the condition acted for a relatively short period and are not now operative.

No treatment that was given during the acute attacks showed any apparent favorable effect on the course of the disease. The symptomatic supportive treatment may have been of greater value than any attempt specifically to influence the heart rate.

The roentgenograms presented a very unusual picture and in the absence of a definite cardiac disorder it would have been difficult to exclude a primary pulmonary lesion. However, we feel justified in assuming that the disturbances in the respiratory system, objectively and subjectively, were a result of the cardiac dysfunction in this instance.

The electrocardiographic tracings do not permit of an accurate distinction between auricular tachycardia and auricular flutter with one to one rhythm. Individual *P* waves may be distinguished but, on the other hand, they may be regarded as part of the flutter cycle which may be discerned if one disregards the ventricular complexes. In an adult the rate would make a diagnosis of flutter almost certain, but when one considers the rapidity with which a normal infant's heart may beat when the child is crying, one must admit that a higher limit ought to be postulated for paroxysmal tachycardia in infants. The significance of the alternation in the size of the *T* wave is also obscure. It has been suggested that such a phenomenon indicates two sources of origin of the heart beat which alternate in the initiation of the excitatory stimulus. There does not seem to be any strong evidence supporting this view. Alternation of the size of the *T* wave with concomitant alternation in size of the *Q-R-S* complex is found in pulsus alternans. We do not think the latter condition was present in this case. It is debatable whether any significance should be attached to the failure to react to vagus stimulation.

Conclusion. 1. A case of extreme tachycardia, of unknown etiology, in a very young infant, is presented with roentgenological and electrocardiographic studies.

2. The course of the disorder was not obviously influenced by treatment.

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A STUDY OF THE VALUE OF INSULIN IN UNDERNUTRITION.

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Insulin has been suggested as a therapeutic agent in a host of non-diabetic conditions. In a discussion of the indications for the use of this drug, Campbell[1] states that "among the thousands of

papers now written on insulin there are some recommending it on quite insufficient grounds for almost every ill to which flesh is heir."

One of the first non-diabetic ailments for which insulin was recommended was malnutrition. In 1923, scarcely a year after insulin was discovered, Pitfield[2] reported good results using insulin in 2 cases of infantile inanition. In the following year Marriott[3] and Barbour[4] reported marked gains in weight in malnourished infants given glucose and insulin. Falta[5] in 1925 was the first to describe the use of insulin in cases of adult malnutrition. He states, "beginning with the first experimental day each of the 3 patients studied developed an enormous appetite which increased to actual ravenous hunger with increasing insulin dosage." With this as a beginning a voluminous literature has accumulated in which insulin is enthusiastically recommended for the treatment of undernutrition resulting from most any cause. Its use especially in thin persons without organic disease is advised by Short,[6] Nichol,[7] Davidson,[8] Metz,[9,10] Barker,[11] Blotner[12,13] and Barron;[14] in malnourished patients with "gastro-intestinal disease or symptoms" by Lueders and Watson;[15] in undernourished tuberculous patients by Arnold,[16] Allen[17] and Heaton,[18] and in psychotic patients by Appel, Farr, and Marshall.[19,20]

In the large literature dealing with the subject, one seldom encounters an article discouraging the use of insulin in undernutrition. Tisdall *et al.*,[21] Tezner and Ebel,[22] and more recently Radwin and Brown[23] report poor results from the use of insulin in malnourished children. A follow-up study made by Nichol[24] showed that relatively few of his insulin treated adult patients maintained the weight they had gained. Wilson, Levine, and Gottschall[25] found no fundamental difference in carbohydrate metabolism between normal and marasmic infants, and found no appreciable difference in the amount of carbohydrate burned in infants when they received insulin or when they did not. These workers conclude, therefore, that the use of insulin as a therapeutic agent in marasmic children is not indicated.

The number of satisfactorily controlled investigations of the value of insulin in undernutrition is conspicuously small. Rarely has the effect of insulin been noted separate from that of the improved diet which is simultaneously given. Nor has there been sufficient study of the possibility that benefit observed during the administration of insulin and attributed to this drug, may be largely if not entirely due to a psychic effect.

It is natural then that one might ask the following questions: 1, If insulin causes a gain in weight, is this accomplished through any action of insulin, *per se*, or is it merely by means of suggestion? 2, Is the gain in weight, if it occurs, brought about by increased ingestion of food, or by better assimilation? 3, Is there any consistent relationship between the level of sugar in the blood and the desire for food? 4, How much of the fattening attributed by many authors to insulin is the result of an improved diet and forced

feeding? 5, Might not a patient, aware that he is receiving insulin, eat more food only because he fears hypoglycemic reactions and knows these can be prevented if sufficient food is ingested?

In an attempt to answer these questions, the following study was carried out.

Method. All patients studied were thin persons who complained of poor appetites. Some had no organic disease, others suffered from tuberculosis. Their ages varied from 13 to 44 years. No patients recovering from an acute illness or surgical operation, who ordinarily would have an improving appetite, were studied. Each patient was weighed at frequent intervals under the same conditions (in the morning, before eating or drinking, and after emptying his bladder). The caloric intake of the patient was computed each day. This was done in the following manner. The calorific value of *all* the food presented to the patient during 24 hours was estimated; from this the calorific value of the food not eaten was subtracted; the difference represents his daily caloric intake. Since the same person (a graduate dietitian supervising the therapeutic diets served in the University Hospital) made all these computations, the method is entirely satisfactory for comparative purposes.

The study is divided into two parts.

I.

Plan of Study. During this portion of the investigation no effort was made to fatten the subjects. After observing the caloric intake and weight for a length of time satisfactory to serve as a control period, insulin was injected 30 to 60 minutes (in most cases 45 minutes) before each of the three meals. The patient, however, was not told why he was receiving injections, nor did he know that the medicine was insulin. In fact, special care was taken that the patient have not the slightest suspicion that an appetite response or increased consumption of food was expected. For this reason their general management remained unchanged. The same type of diet and plan of feeding that was used prior to the period of study was continued.* More food was served, however, than the patient had been eating and if at any time still more food was requested, it was generously supplied. These precautions were taken to make certain that the patient would have no difficulty in satisfying his appetite or appeasing his hunger.†

In order to make sure that a sufficient amount of insulin was being given to serve as an adequate test, the dosage was gradually increased from the initial dose of 3 or 5 units until mild hypoglycemic reactions occurred in many patients. Extreme care was taken, however, that no harmful insulin reaction occur. All attend-

* Those who had been receiving only 3 meals a day were similarly served during the experimental period. Those having interval feedings previous to the study continued to receive them.

† Throughout this article, *appetite* is referred to in the sense that Cannon[26] uses it to designate a *pleasurable* desire to eat, in contrast to *hunger* which is referred to as a *painful* sensation that experience has shown can be relieved by partaking of food.

ants were instructed to be vigilant for any sign of hypoglycemia, and should a reaction occur, to treat it at once.

Using this procedure, the possibility of the patient increasing his consumption of food in order to prevent hypoglycemic reactions was eliminated, and an increase in one's desire for food as a result of insulin might be observed unassociated with any psychic effect.

TABLE 1.—THE RESULTS OF ADMINISTRATION OF INSULIN TO THIN PATIENTS WHO DID NOT KNOW THEY WERE RECEIVING INSULIN OR THAT AN INCREASE IN APPETITE OR HUNGER WAS EXPECTED TO ACCOMPANY THE INJECTIONS.

Patient.	Age.	Sex.	Diagnosis.	Length of time insulin was administered.	Dosage of insulin at time injections were stopped.	Hypoglycemic reactions.	Total change in weight while receiving insulin.	Average daily caloric intake while receiving insulin.	Appetite or hunger.
				(Days.)	(Units.)			(Calories.)	
H. S.	21	M	Pulmonary tuberculosis and tuberculosis of hip (afebrile)	19	10–10–10	None	Lost 1.2 kg.	1880 (No change during insulin period)	Reported no change.
J. M.	18	M	Pulmonary tuberculosis (minimal) (afebrile)	17	7–7–7	On 2 occasions	Gained 0.6 kg. (same rate of gain prior to insulin)	1863 (No change while receiving insulin)	No improvement in appetite; hunger did not accompany hypoglycemia.
J. J. M.	19	M	Pulmonary tuberculosis (afebrile)	45	16–16–16	.....	Gained 1.2 kg. (less than rate of gain prior to insulin)	2110 (Less than before and after insulin)	No change.
L. D.	39	F	Pulmonary tuberculosis (afebrile)	26	8–8–8	3 definite reactions	Lost 0.4 kg. (gained 2.3 kg. in 45 days after insulin was stopped)	1289 (1525 after insulin was stopped)	No change; not hungry during insulin reaction.
M. A.	29	F	Psychoneurosis	18	20–20–20	1 moderately severe	Lost 0.6 kg.	1074 (1111 after insulin was stopped)	No change.
F. W.	19	F	Psychoneurosis	10	15–15–15	1	Lost 0.7 kg.	721 (863 after insulin was stopped)	No change; not hungry during insulin reaction.
J. W.	19	M	Pulmonary tuberculosis	14	6–6–6	None	Lost 0.2 kg.	2351 (No change during insulin)	No change.
S. P.	18	M	Pulmonary tuberculosis (afebrile)	18	9–9–9	None	Gained 2.1 kg. (gained 1.7 kg. during 17 days prior to insulin)	2970 (2590 prior to insulin)	"Appetite improving."
T. J.	31	M	Psychoneurosis	8	15–10–10	.....	Gained 2.5 kg. (gained 2.2 kg. in 4 days prior to insulin)	3200	"Good appetite."

Results. In this way the effect of insulin was observed in 9 patients. A summary of the results is shown in Table 1. Of the 9 subjects studied, 7 had no increase in appetite, food consumption, or rate of gain in weight. Five of these 7 actually lost weight during the administration of insulin. Two gained weight; J. M. at a rate equal to the gain prior to insulin therapy, and J. J. M. at a rate

slower than during the period before insulin was given. The table shows the continued low caloric intake in these 7 patients. Patient S. P. gained weight at a rate slightly more rapid than before insulin was given, and his caloric intake was noticeably increased. He felt that his appetite was improved. Patient T. J. gained 2.5 kg. in the 8-day period during which he received insulin, but it should be noted that during the 4 days just before insulin was administered he gained 2.2 kg.

II.

Plan of Study. In the second part of this study an attempt was made to fatten the subjects, and to measure separately the effect of (1) a high caloric diet, (2) suggestion accompanying injections, and (3) insulin. In this way, it would be possible to determine whether or not insulin, by reason of any pharmacologic effect, is a therapeutic aid in fattening thin persons.

To accomplish this purpose the following procedure was adopted: A high caloric diet was instituted. For control purposes, a diet identical day after day throughout the study would be desirable, but because the monotony of this might cause a decrease in appetite, the patients were given their choice of food rich in energy for three meals a day, and in addition high caloric interval nourishments were served. Each patient was served more food than he had been eating previously. Additional food was supplied at any time the patient wished it. Thus the patient could eat all he desired. This dietary and manner of feeding remained unchanged throughout the entire period of study.

The caloric intake and changes in weight were observed for a control period (usually 2 or 3 weeks) after starting this diet. Subsequently, injections were given 30 to 60 minutes (usually 45 minutes) before each of the 3 main meals. When the injections were started the patient was enthusiastically told that he was being given these injections because there was reason to believe they would whet his appetite, make him hungry, and thus increase his consumption of food and improve his state of wellbeing. However, in order to determine how much psychic effect was produced, sterile water or saline was injected for a period of 2 or 3 weeks. Then, at a time unknown to the patient, insulin in increasing doses was substituted for the placebo. The dose of insulin was increased in almost every instance until one of the following effects was noted: (1) until an improvement of appetite or hunger was noted and reflected by increased consumption of food and rate of gain in weight, (2) until any undesirable reaction from insulin was noted, or (3) until the noon blood sugar was recorded at a low level (see below). So, although the patient knew an improvement of appetite and increased food consumption were expected, he did not know when insulin

was being injected. The same care to avoid harmful reactions from insulin was exercised.

During the period when insulin was being given, frequent sugar determinations, by the method of Folin-Wu,[27] were made on blood obtained at 12 o'clock noon, just before the patient began his midday meal. In this way, it was hoped to learn whether or not any increased desire for food resultant from insulin need be associated with hypoglycemia. A noon blood-sugar determination was made at the beginning of the study to serve as a control.

Results. The results of the second portion of this study can best be shown graphically. The accompanying figures (1 through 8) show the response in 8 of the 11 individuals studied in this way.

Explanation of Graphs. The age, sex, and diagnosis of the patient appear on each graph. I. W. represents the "ideal weight"* in each case. The patient's weight and daily caloric intake are plotted on the upper and middle third of each graph, respectively; in the lower third the total daily insulin dosage (I) is shown by a line and the noon blood-sugar level (B. S.) represented by a cross (X). Insulin reactions are indicated by an R in the portion of the graph where insulin is plotted. In some cases the weight record prior to the period of study is shown. Each graph is divided into panels showing the response to (1) diet only, (2) to the same diet plus sterile water (S. W.) or sterile saline (S. S.), and (3) to the same diet plus insulin. The numbers in the weight and caloric intake spaces indicate the average daily weight change in grams, and the average daily caloric intake in each case. The average daily caloric intake for the different periods is also represented graphically.

Clinical Data. Two patients, one a girl, A. B., aged 13, with renal and pulmonary tuberculosis (afebrile), the other a boy, I. M., aged 14, having widespread pulmonary tuberculosis (afebrile) both markedly undernourished and having poor appetites failed to respond in any way to diet, placebo, or insulin, even though the latter was given in doses sufficiently large to cause mild hypoglycemic reactions in each case, and to lower the noon blood sugar to 44 mg.% in the girl and to 55 mg.% in the boy. There was no subjective improvement in either patient. Since the response is practically identical in each case, a graph is shown for only the girl (Fig. 1).

Figure 2 shows the response of Miss C. W. There was a beneficial response to the increased diet, a slight additional improvement when a placebo was given, and a falling off of caloric intake and decreasing rate of gain during administration of insulin. There was no subjective response accompanying the administration of insulin.

Miss M. B. (Fig. 3) was benefited by the diet alone. Added benefit occurred when placebos were given. When insulin was used there was no significant change. This patient reported that her appetite was better as soon as she began receiving placebos. The first day she received 13 units of insulin before each meal she said she felt hungry before breakfast, but on that day the caloric intake did not change significantly.

Observations made on Miss L. P. are shown in Figure 4. Again, a distinct improvement resulted from feeding a high caloric diet, and an unques-

* "Ideal weight" here refers to the *average* weight for a normal individual of the patient's sex, age and height.

tionable additional benefit from placebos. An actual decrease both in caloric intake and rate of gain occurred when insulin was administered. This patient stated that her desire for food seemed greater when she began receiving placebos. At no time during the administration of insulin did she report any subjective change.

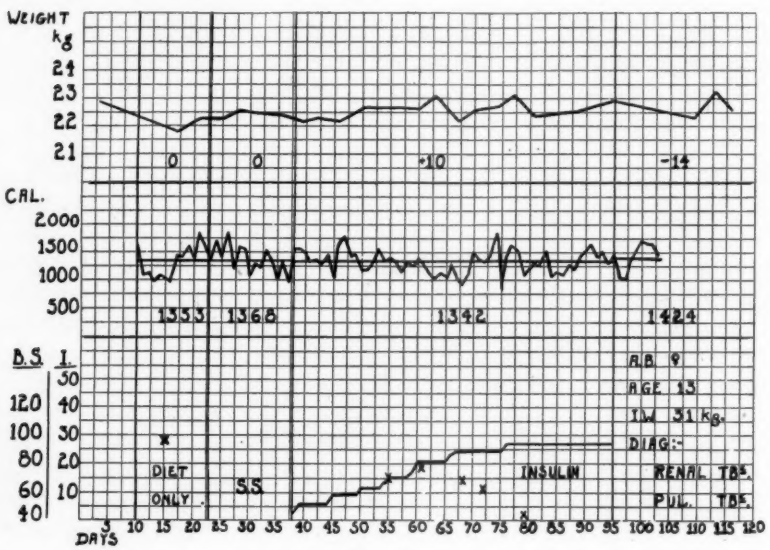

FIG. 1

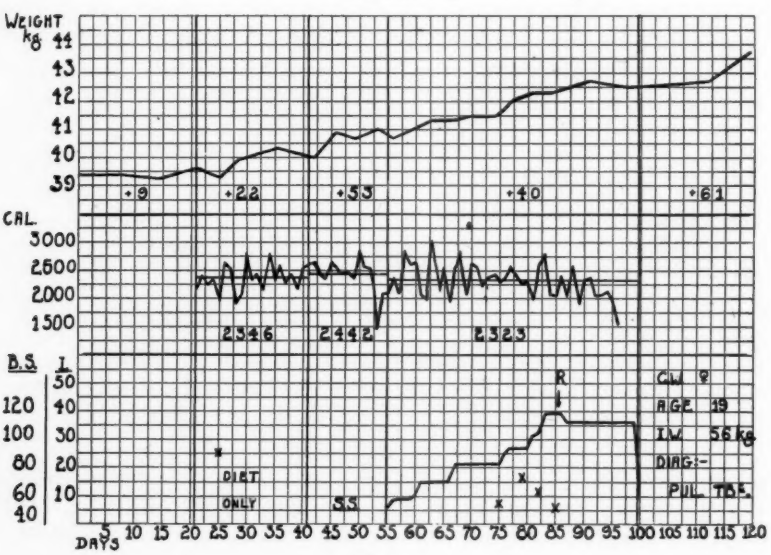

FIG. 2

When studying Miss V. H. (Fig. 5) a slight variation in procedure was made. After demonstrating a slight gain in weight on the diet alone, place-

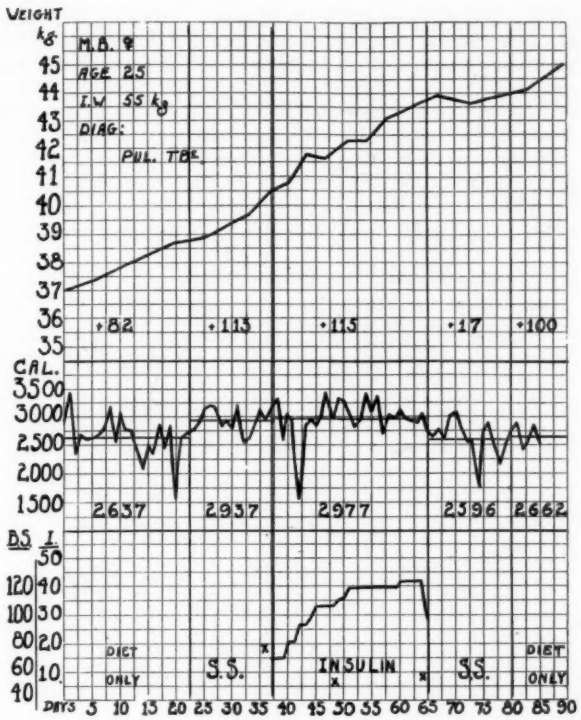
WEIGHT
Kg
M.B. ♀
AGE 25
I.W. 55 Kg
DIAG:
PUL. TBC.
+82
+113
+115
+17
+100
CAL.
2637
2937
2977
2396
2662
B.S. I.
DIET ONLY
S.S.
INSULIN
S.S.
DIET ONLY
DAYS

FIG. 3

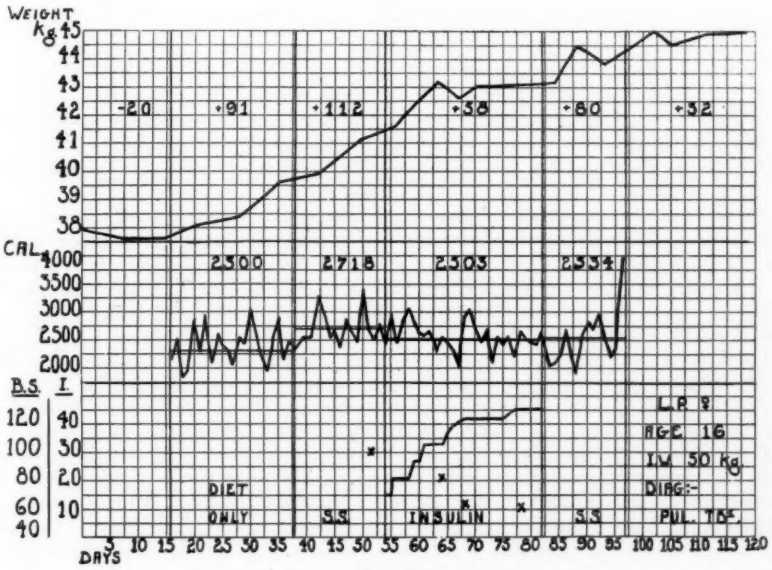
WEIGHT
Kg
-20
+91
+112
+58
+80
+32
CAL.
2500
2718
2303
2334
B.S. I.
DIET ONLY
S.S.
INSULIN
S.S.
L.P. ♀
AGE 16
I.W. 50 Kg
DIAG:-
PUL. TBC.
DAYS

FIG. 4

bos were given. When these were started the patient was not told why the injections were being given. There was a falling off of the caloric intake. The patient was then told that these injections were given to increase her desire for food. She promptly reported an improved appetite and her food consumption increased noticeably so that the average daily caloric intake was decidedly higher than it was during the period of high caloric diet alone. When insulin was substituted no significant change in caloric intake occurred. She reported a feeling of *hunger* at times just prior to meals, when the insulin dosage was high. No *appetite* change accompanied the use of insulin in this patient. She disliked all injections.

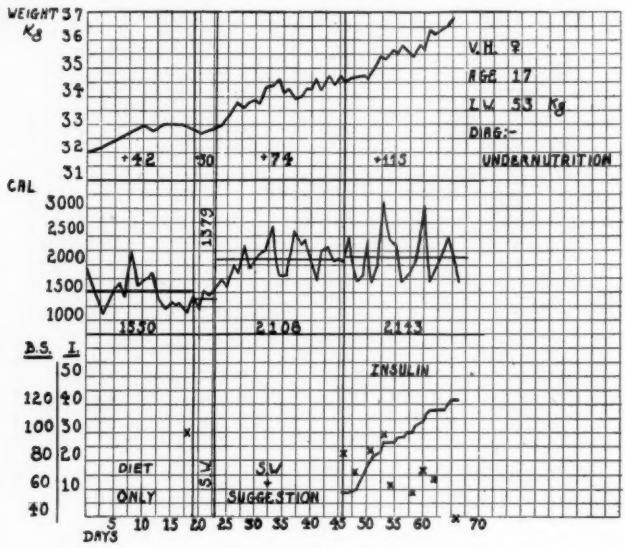

FIG. 5

Mrs. M. P. (Fig. 6) was distinctly benefited by the administration of placebos. There was an additional increased consumption of food during the period when insulin was given. Because of her neurosis, subjective change could not be evaluated in this patient.

A 17-year-old girl, Miss D. G. (Fig. 7), responded well to the improved diet. She, however, greatly disliked injections, and showed a decreased food intake and stationary weight when normal saline was injected. When insulin was begun there was a prompt lowering of blood sugar and the patient reported having a feeling of hunger prior to the morning and noon meals, and a good appetite for all meals. Unfortunately figures for her caloric intake during the early part of the insulin period have been lost; nevertheless, the weight curve shows prompt gain in weight, and the average caloric intake over the latter part of this period shows distinct increase in food consumption. It should be noted, however, that the average daily caloric intake and gain in weight are essentially the same as when she received the high caloric diet alone. The prompt lowering of caloric intake when insulin was stopped and placebos substituted suggest, however, that insulin might have been of benefit to this patient.

One of the most interesting patients studied was Mr. R. R. The data in his case over the long period of study are shown in Figure 8. Diet alone

was not successful in fattening this patient. When placebos were given a slight benefit resulted. A decided additional advantage was noted when insulin was injected. The patient stated that he had a better appetite and frequently felt hungry before meals when insulin was given. Subjective and objective improvement ceased when sterile water was substituted for insulin. After these observations were made it was decided to carry out

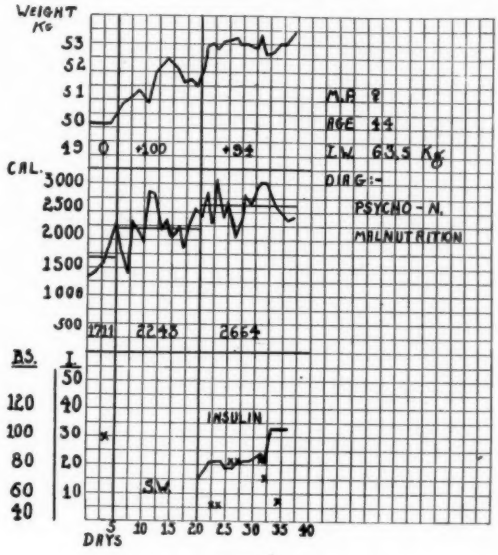

FIG. 6

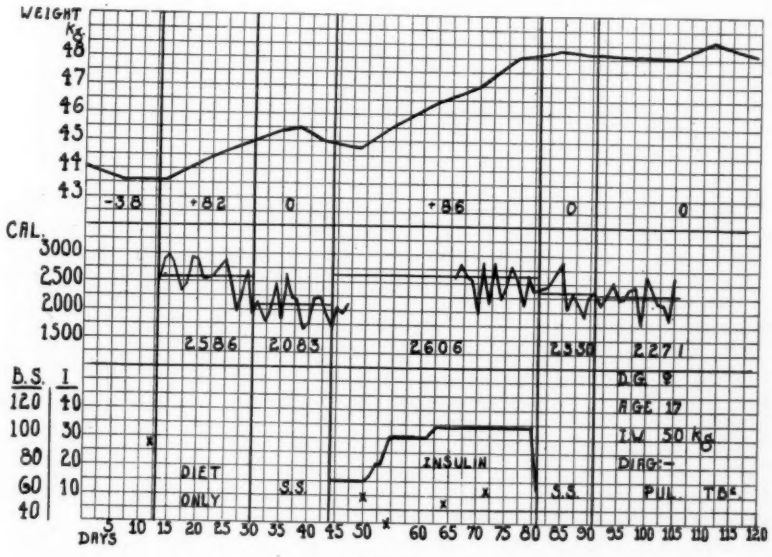

FIG. 7

the same study again on this patient. Accordingly, after another control period of diet alone, sterile water was again injected. There was a repetition of the slight benefit previously noted with the administration of placebos. Interestingly enough, however, when insulin was given the second time no increase in caloric intake occurred, and the weight curve did not change. (The average daily gain in weight as calculated is greater, but it so happens that both at the beginning and at the end of the period the fluctuations normally occurring in one's weight were such to produce this erroneous figure. Inspection of the weight curve from the 80th to the 155th day shows it to follow a straight line.) There was no subjective change during this second period of insulin. This lack of response is the more interesting when it is seen that the noon blood-sugar levels during the second insulin period were lower than during the first insulin period, and that the patient's weight is still far below his "ideal weight."

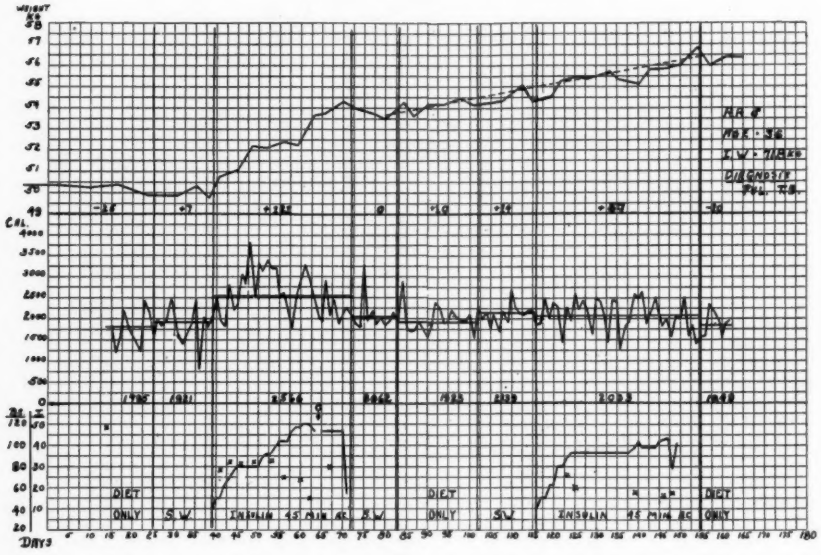

FIG. 8

Charts are not reproduced for the last 2 patients studied. Mrs. E. H., aged 41, who had chronic arthritis, and latent lues, was 19 kg. under her "ideal weight." She gained nicely on the diet alone. Her average consumption was 2643 calories daily. During the time she received sterile saline, she consumed an average of 2872 calories daily with a corresponding increase in gain in weight. During the short time she was receiving insulin (5 days), but in amounts sufficient to lower the noon blood sugar to 56 mg. %, she consumed an average of 2875 calories and gained weight at a rate slightly less than when receiving placebos. There was no important subjective change in her case.

The last patient studied, Miss D. R., aged 22, whose diagnoses were psychoneurosis and malnutrition, weighed only 27.4 kg. Her "ideal weight" was 50 kg. On the diet she gained only slightly. She objected severely when injections of sterile water were started and seemed to revolt against eating. Her average daily caloric intake fell from 1580 to 926. When insulin was given the average daily consumption was only 819 calories.

Insulin, which was started in 3 unit doses and increased to 8 units t.i.d., was stopped after 8 days because of her continued objection to injections even though she understood they were given in an attempt to improve her appetite. On the day insulin was stopped, a 5% glucose solution was given intravenously because her food consumption was so small. She disliked the intravenous therapy sufficiently that in order to avoid being given more infusions, the very next day she consumed 2100 calories and maintained an average daily intake of 2157 calories for the remainder of her stay in the hospital. She gained weight correspondingly.

A summary of the results of the second part of the investigation appears in Table 2.

TABLE 2.*—RESULTS OF ATTEMPT TO FATTEN PATIENTS FIRST WITH A HIGH CALORIC DIET, NEXT WITH DIET AND PLACEBO, AND LASTLY WITH DIET AND INSULIN.

Patient.	Benefit from high caloric diet only.			Additional effect of placebo.				Additional effect of insulin as compared with diet plus placebo.			
	None.	Slight.	Good.	Worse.	No change.	Benefit.		Worse.	No change.	Benefit.	
						Slight.	Good.			Slight.	Good.
A. B.	+	..	..	..	+	..	..	..	+		
I. M.	+	..	..	..	+	..	..	..	+		
C. W.	..	+	..	..	..	+	..	Slightly			
M. B.	..	..	+	..	..	..	+	..	+		
L. P.	..	..	+	..	..	..	+	+			
V. H.	..	+	..	..	..	..	+	..	+		
M. P.	+	..	..	..	..	..	+	..	..	..	+
D. G.	..	..	+	+	..	..	..	..	..	..	+
R. R.	+	..	..	..	..	+	..	..	..	..	+
(Repeat)	+	..	..	..	..	+	..	..	+		
E. H.	..	..	+	..	..	+	..	..	+		
D. R.	..	+	..	+	..	..	..	..	+		
Total†	4	3	4	2	2	3	4	2	6	0	3

* This table is based primarily on a comparison of the daily caloric intake, with which the changes in weight very closely agree.

† Excluding repeat study in R. R.

Discussion. The results of this study do not substantiate the claim that insulin is a valuable adjunct in the treatment of undernutrition. No appreciable benefit occurred in 8 of the 9 patients first studied, who were injected with insulin without their knowing what medicine was being given or why it was administered. Mr. S. P. was the only subject in the first group who showed an increased rate of gain in weight when insulin was administered, and it should be noted that prior to insulin therapy he consumed enough food to cause him to gain weight at the rate of 100 gm. a day. Only 3 of the 11 subjects of the second part of the study showed a response that might be attributed to insulin. In 1 of these 3 patients, Miss D. G., the response to insulin was decidedly better than that to a placebo, but no better than the response to the high caloric diet alone; and

in another, Mr. R. R., the very definite improvement noticed when insulin was first administered did not occur during the second period of insulin therapy. In 6 patients of the second group there was no significant change in caloric intake or weight when insulin was substituted for a placebo, and in 2 the benefit was actually less when insulin replaced the placebo. Only 2 patients of the entire study then showed any improvement that could certainly be attributed to insulin. No patient showed remarkable improvement during the administration of insulin and ravenous hunger reported by so many writers was not once observed.

One wonders how insulin might be beneficial, if it is, when administered to undernourished patients. Okada *et al.*[28] have shown that the injection of insulin increases gastric, biliary and pancreatic secretions. Lueders and Watson[15] measured an increase in concentration of pancreatic ferments recovered from malnourished patients when insulin was given. These authors felt that the patient's gain in weight was due in part to an improvement in digestion and assimilation of food elements which resulted from the increased concentration of pancreatic enzymes and bile. The fact that there is such close correlation between the caloric intake (ingestion) and changes in weight of the patients herein reported shows that during insulin therapy there certainly was no important increase in absorption or utilization of food, but rather that the digestion, absorption and metabolism of food remained unaffected, and whatever increase in weight that occurred during the administration of insulin resulted from increased ingestion.

Bulatao and Carlson[29] found that when insulin is injected into normal dogs, "gastric hunger contractions and gastric tonus are augmented to the point of incomplete gastric tetany when the blood sugar falls to 0.085 to 0.075 mg.%." Later, Quigley, Johnson, and Solomon[31] reported that when normal fasting human subjects were injected with 12 to 20 units of insulin an increase in gastric tonus and hunger contractions, and a prolonged hunger period resulted. They suggest that it may be this effect of insulin on the stomach which leads to an increased ingestion of food that accounts for the gain in weight accompanying the administration of insulin to persons with anorexia. The results obtained in this study conform to this view. The close correlation between changes in weight and caloric intake, and the subjective sensation of hunger, when the dosage of insulin was sufficient to cause a distinct fall in blood sugar, surely favor this explanation for the beneficial effect of insulin when it occurs. Because this response occurred in the minority of patients studied and because reactions to insulin were frequently observed without an accompanying sensation of hunger it appears that this effect of insulin does not uniformly occur, or may be present for such a short time that it is ineffectual as a stimulus to increase food consumption.

That there is undoubtedly an important psychic factor in many of the patients to whom injections were given is demonstrated by this study. There was a decided lack of beneficial effect of insulin when it was given to patients ignorant of the nature of the medication and the results expected. On the other hand, definite improvement was noted subjectively and objectively in several of the patients expecting benefit from injections when the substance injected was only sterile saline or water. There can be no doubt that the improvement which accompanied the injections of saline in patients M. B., L. P., V. H., and M. P. would have been attributed to insulin had this drug been injected without a preliminary control period of saline injection. There has been insufficient evaluation of this psychic effect, which is often great, and which may in some cases account for the entire improvement noted.

That benefit commonly credited to insulin belongs in part to concurrent improvements of the dietary is amply shown in the latter half of this study.

Conclusions. 1. This investigation fails to support the prevalent opinion that insulin is a valuable aid in the treatment of undernutrition.

2. When undernourished patients were injected with insulin and its effect noted separately from diet and suggestion the great majority of patients failed to show any response. The improvement which was attributable to insulin in 2 cases was small.

3. The fact that improvement resulted in many patients from the *suggestion* accompanying injections, indicates that much of the benefit commonly attributed to insulin is due to a psychic factor.

The author is deeply indebted to Dr. L. H. Newburgh for many helpful suggestions made during the progress of this investigation, to Miss Mary Stanley for the blood-sugar determinations, and to Miss Gladys Enke for computing the daily caloric intake of the patients studied.

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(Titles have been omitted for sake of brevity.)

FULMINATING HEMORRHAGIC ENCEPHALITIS.

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In the numerous papers on encephalitis published during the past few years, little or no mention has been made of the rapid and fatal course the disease may take. It is the purpose of this communication to call attention to the fulminating type of encephalitis which terminates in unexpected and sudden death.

The clinical histories and autopsy findings of 5 cases of encephalitis are recorded. Unusual features, and the justification of the term "fulminating" encephalitis, are emphasized.

In every instance an autopsy was performed a few hours after death. The brain was preserved in formalin for 2 weeks before it was examined. Sections of the brain taken from various portions were stained with hematoxylin and eosin. Davenport's method was used for the study of the axis cylinders, the Weil method for the staining of the myelin sheaths, and Holzer's stain for the study of glia fibers. The von Gieson stain was used when deemed necessary.

Case Abstracts. Case 1.—A white male infant, aged 4 months, was perfectly well until the day of his death. On that day, while out with his nurse, he developed signs of dyspnea as if he had inhaled a foreign body.

He was hurried home and a pulmotor squad was called, but he became markedly cyanotic and died.

Necropsy revealed a well-developed and well-nourished infant. The lymph nodes, particularly the mediastinal and peritoneal, were larger than normal. The follicles and Peyer's patches throughout the gastro-intestinal tract were hyperplastic. The thymus weighed 55 gm. Both lungs revealed a very recent bronchopneumonia. The aorta was hypoplastic. There were 3 accessory spleens. The brain was markedly hyperemic. On section, the white and gray substances appeared reddish, and petechial hemorrhages were found throughout the white substance. Hemorrhages were also noted in the pons and cerebellum.

Histologic examination of the brain revealed a marked dilatation of the smaller vessels, which were packed with red blood corpuscles. Many perivascular spaces contained red blood corpuscles. Extravasation of these cells was more pronounced in the region of the third and fourth ventricles. Lymphocytes and a few neutrophils were also found in the perivascular spaces.

The *anatomic diagnosis* was acute catarrhal bronchitis; recent bilateral bronchopneumonia; very early acute hemorrhagic encephalitis; enlarged thymus; generalized lymphoid hyperplasia; marked hyperplasia of the follicles and Peyer's patches of the gastro-intestinal tract; three accessory spleens.

Summary of Case 1. Inasmuch as the autopsy revealed a marked increase in the lymphadenoid tissue throughout the body, as well as a large thymus, it is possible that this child belonged to the group classified as status thymico-lymphaticus. This may explain the lowered resistance of the child and the reason he succumbed so rapidly to the acute infectious disease. We shall return to this later. The cause of death, in our opinion, was an acute hemorrhagic encephalitis, with the recent bronchitis and bronchopneumonia as the portal of entry of the etiologic agent. In other words, the child, whose resistance had been low since birth, developed bronchitis and bronchopneumonia and an acute inflammation of the brain from which he died.

CASE 2.—A white female child, aged 29 months, was admitted in a moribund state. Three hours prior to admission the patient's parents heard her calling and found her in convulsions. The temperature was 107°. The child was rushed to the hospital. Diffuse clonic convulsive movements of all extremities were present. The neck was rigid and the pupils were fixed and dilated. The skin was covered with purplish-red blotches. The temperature on admission was 106°. A lumbar puncture yielded 20 cc. of a clear, colorless fluid. The fluid contained 11 white blood cells, 5 of which were neutrophils and 6 lymphocytes. One hundred and fifty red blood cells were present. The Pandy test was negative. The sugar content of the cerebrospinal fluid was 85 mg. per 100 cc.

The child had previously been well. She had had no symptoms of a cold, sore throat or other ailment prior to the onset of the disease.

The course was steadily downhill. The child did not improve following the administration of sedatives and died 1½ hours after admission to the hospital.

Necropsy revealed a recent bronchopneumonia in portions distinctly hemorrhagic. The aorta was hypoplastic. There was a fatty metamorphosis of the liver and a cloudy swelling of the kidneys. The follicles of the

spleen were very prominent. The thymus weighed 65 gm. and revealed minute hemorrhages. The Peyer's patches and the lymph follicles in the small and large intestines were very prominent. The cortical vessels were markedly hyperemic. The gyri were flattened and swollen and the sulci were narrowed. On section, the white substance of the brain was pinkish and its differentiation from the cortex indistinct. Many petechial hemorrhages and dilated capillaries were seen throughout the white substance of the brain.

The *histologic examination* of the lungs revealed some alveoli filled with neutrophils, mononuclear and red blood cells and phagocytic cells containing brown pigment granules. The Gram-Weigert stain revealed the presence of bacteria arranged in groups of two.

Sections of the brain showed, in many places, a distinct extravasation of red blood corpuscles into the perivascular spaces. Occasionally a few neutrophils were found in these spaces, as were a number of lymphocytes. Some of the fields revealed red blood corpuscles in the parenchyma, apparently not in the vicinity of the vessels. Many ganglion cells had markedly faded nuclei and in many instances, nuclei were not recognizable.

Summary of Case 2. The outstanding feature of this case is the very short duration of the illness, which lasted only about 6 hours. The cause of death was a very acute hemorrhagic encephalitis. The bronchopneumonia was apparently of longer duration than the encephalitis. Sections of the lungs contained diplococci. Bacteria were not found in the brain.

Case 3.—The essential points in the history of this white male child aged 9 months, were a cough which had persisted for 3 days, convulsions which had begun 10 hours before admission, drowsiness, heavy breathing, stridor, generalized rash and cyanosis of 10 hours' duration. Except for the cough, the child had been well until the day before admission to the hospital, when he had refused to eat.

On admission, the child was acutely ill. There was marked inspiratory stridor. The patient's temperature was 105.8°, pulse 160, respirations 58. His pupils were fixed and there were petechiæ in the conjunctivæ. The right ear drum was red, the pharynx hyperemic and the tonsils were enlarged. The neck was not rigid. The heart was normal. There was a marked sternal retraction during inspiration. Bronchial breathing could be heard over the right lung, as could crepitant râles on both sides; all sounds, however, were obscured by the inspiratory stridor. Petechiæ were present over the face, neck, chest and extremities. The face and extremities were cyanotic.

The impression on admission was bilateral bronchopneumonia; toxemia, secondary purpura; probable encephalitis.

The child was put into an oxygen tent. His respiration and pulse became more rapid and he died 2 hours after admission to the hospital. No laboratory work was done.

Necropsy revealed a bilateral bronchopneumonia. The lymph nodes throughout the body and the solitary follicles and Peyer's patches in the gastro-intestinal tract, were enlarged and hyperemic. The thymus weighed 45 gm. There were petechial hemorrhages in the pleuræ, pericardium, intestinal mucosa, bladder, pelvis and skin. The brain was markedly hyperemic and minute petechial hemorrhages were seen throughout the white substance, especially in the region of the left basal ganglia. Petechiæ were also seen in the left dentate nucleus. There was slight hemorrhage in both suprarenals.

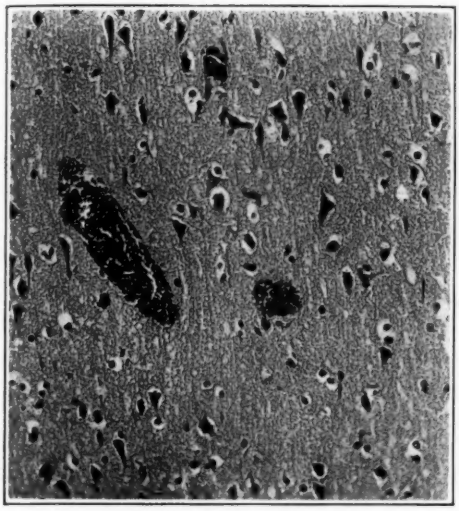

FIG. 1

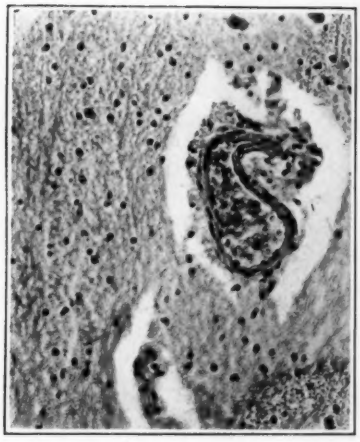

FIG. 2

FIG. 1.—Case 1. Early acute hemorrhagic encephalitis. Note the hemorrhages in the perivascular spaces. Hematoxylin and eosin. (150 ×.)

FIG. 2.—Case 1. Note the perivascular infiltration. Hematoxylin and eosin. (180 ×.)

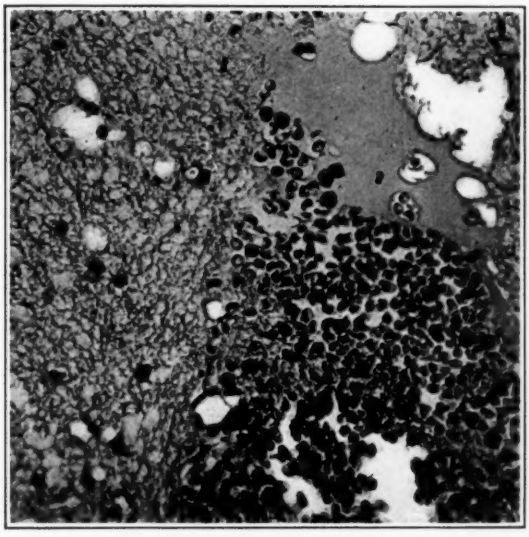

FIG. 3.—Case 2. Note the red cells with a few neutrophils free in the tissue. Hematoxylin and eosin. (380 ×.)

ICH.

FIG. 4

FIG. 5

FIG. 4.—Case 3. Note the hemorrhage and the neutrophils. Hematoxylin and eosin. (260 ×.)

FIG. 5.—Case 5. Note the perivascular infiltration of neutrophils. Iron-hematoxylin and eosin. (240 ×.)

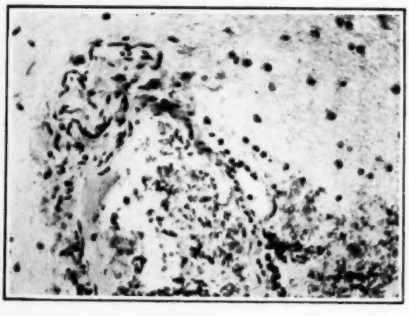

FIG. 6

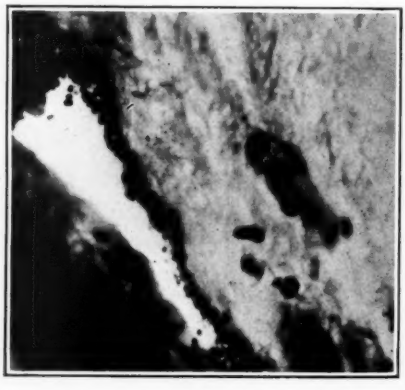

FIG. 7

FIG. 6.—Case 5. Perivascular infiltration of neutrophils and perivascular hemorrhage. Iron hematoxlyin and eosin. (180 ×.)

FIG. 7.—Case 5.—Cocci with the bloodvessel and wall. Gram Weigert. (600 ×.)

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Microscopic section through the brain revealed the following histologic changes: The large and small bloodvessels, particularly the capillaries, were distended with red blood corpuscles; many red cells were found free in the perivascular spaces. In places, some of the small bloodvessels were surrounded by lymphocytes and only very occasionally were neutrophils found. Minute accumulations of lymphocytes were seen throughout the cortical portions of the brain. The ganglion cells showed a marked granularity of their cytoplasm and in many instances the nuclei were absent.

Summary of Case 3. The chief interest of this case lies in the short duration of the illness. As has been mentioned above, the child felt fairly well until the evening preceding his admission to the hospital, when he suddenly became drowsy. He died the day he was admitted to the hospital. The cause of death was acute encephalitis.

CASE 4.—A white female, four and a half years of age, had been well until she contracted whooping cough, which had lasted 2 weeks and was relatively mild. She ate and slept fairly well until 24 hours before admission to the hospital, when her mother noticed that she was restless during the night and seemed apathetic. The next day, the child's face seemed asymmetrical.

Physical examination after admission to the hospital revealed a right facial paresis and weakness of the right leg. The patient was rational. The following morning, about 30 hours after the onset of the illness, she had clonic and tonic convulsions and was unable to talk. Definite paralysis of the right side was noticed at that time. There was but a slight elevation of temperature during the period of hospitalization, not higher than 100.4° rectally. The urine contained glucose and a trace of albumin.

The child died 48 hours after the onset of the symptoms, with signs of respiratory paralysis. A spinal puncture, performed the day the convulsions occurred, yielded clear fluid under increased pressure, with but 5 cells per c.mm.

Necropsy (confined to the brain). The brain was markedly hyperemic. Petechial hemorrhages were found in the region of the frontal lobe. Minute hemorrhages were found throughout the cut sections of the brain; these were more pronounced in the region of the left orbital and frontal lobes. The subarachnoid space contained a small amount of serous liquid.

On *histologic examination*, neutrophils and a few lymphocytes and endothelial cells were found in the subarachnoid space. About the bloodvessels within the brain tissue was found a network of homogeneous pink-staining material, in the meshes of which were red blood corpuscles, neutrophils, endothelial cells, lymphocytes, and nuclear débris. Foci of neutrophils, lymphocytes and endothelial cells, in addition to accumulations of red cells, were also found within the brain, but not in relation to bloodvessels.

Summary of Case 4. Because of the more severe involvement of the brain than of the meninges, we are of the opinion that the encephalitis was primary and the meningeal reaction secondary.

CASE 5.—A 37-year-old white male was admitted to the hospital at an early morning hour and died the same day. The patient was apparently well previous to the onset of his illness. At midnight, he had been awakened by his wife and asked to attend to their child, who had whooping cough. He was apparently rational at the time and went back to bed. At 1.45 A.M., his wife was awakened by his stertorous breathing. She was unable to rouse him. On admission to the hospital, the patient was in deep coma,

with Cheyne-Stokes respiration and generalized cyanosis. The lungs were apparently normal, the heart regular and the pulse rate 100 beats per minute. The arterial blood pressure ranged from 125 to 195 systolic and from 80 to 100 diastolic. There were definite periods of apnea. Except for the abdominals, the reflexes were completely absent. There was a marked cyanosis. There was no evidence of facial paralysis and no rigidity of the neck.

Spinal puncture yielded clear fluid under slightly increased pressure. It contained about 100 crenated red cells, but no white cells. The Wassermann, Nonne, and Ross-Jones tests were negative. The leukocyte count at that time was 32,000, the red blood cell count 5,350,000, hemoglobin 90%. The urine showed traces of albumin and glucose; there was neither acetone nor diacetic acid; the specific gravity of the urine was 1020. The patient's temperature gradually rose to 101.2°, his pulse increased to 120 beats per minute. His respiration continued to be Cheyne-Stokes in character and periods of apnea occurred every 50 to 70 seconds. Just before death, the patient's respiration became more labored and decreased to 6 per minute. He died 20 hours after the onset of the illness.

Necropsy revealed bilateral hemorrhagic bronchopneumonia; healed endocarditis of the mitral valve; moderate arteriosclerosis of the aorta and coronaries; and slight myocardial fibrosis. There was also a healed apical tuberculosis. The surface of the brain was bluish-purple; the gyri were markedly flattened, the sulci obscured. The subarachnoid vessels were hyperemic. The hyperemia was especially pronounced in the region of the cerebellum and pons. The internal capsule seemed much darker than normal. The basal ganglia also seemed darker than normal and appeared somewhat granular. Markedly dilated vessels and minute petechial hemorrhages were seen throughout the entire white substance of the brain.

Microscopic examination of the brain revealed a variety of changes. The bloodvessels throughout, and particularly the capillaries, were packed with red cells, the outlines of which were clearly recognizable. In many sections there was a distinct extravasation of red blood corpuscles into the perivascular spaces. Some of the sections also revealed foci of hemorrhage without any recognizable bloodvessels in these particular regions. Some of the bloodvessels showed small rings of a hyalin-like material lining their inner walls. Other sections showed many neutrophils at the periphery of the lumen of the vessels and also infiltrating their walls. In many instances, a distinct perivascular infiltration of neutrophils could be made out. These changes were seen throughout the gray and the white substance, but were more pronounced in the latter. Sections taken through the basal ganglia also revealed a marked hyperemia and extravasation of red blood cells. In addition to these changes, however, many ganglion cells without any recognizable nuclei were seen. In some instances, the cytoplasm of these was granular; in others it seemed to be arranged in clumps. Other ganglion cells were completely transformed into hyalin-like globules. In some instances, but especially noticeable within the pons, cerebellum and locus cæruleus, a few bloodvessels were surrounded by lymphocytes. Here and there a few clumps of blood pigment granules were also noted. Other sections showed an apparent atrophy of rows of ganglion cells with pyknotic nuclei. Occasionally, there were seen dark-bluish stained, well-outlined bodies (corpora amylacea). There was also a slight increase in glia cells and fibers in the region of the locus cæruleus, replacing ganglion cells. The Davenport stain indicated a diminution of nerve fibers in these sections. Degeneration of the myelin sheaths was also noted. Cocci were very rarely present within the walls of the vessels. In only one field were they found outside the vessels invading the surrounding brain tissue. The cocci were arranged in groups of two and were Gram-positive.

Summary of Case 5. The short duration of the disease is again impressive. It is of interest that there was but slight clinical evidence of the bronchopneumonia, although it was of longer duration than the acute encephalitis, which we believe was the cause of death. The clinical picture was apparently completely dominated by the encephalitis. The coincidental presence of the acute and old encephalitis will be discussed later.

Discussion. These 5 cases of encephalitis were all fulminating. In one instance, death was sudden; in the others, it occurred unexpectedly within 4½ hours, 12 hours, 20 hours, and 48 hours, after the onset of the illness. The severity of the encephalitis in all of these cases makes us believe that in spite of pneumonia in 4 cases and of whooping cough in the fifth, the cause of death was encephalitis.

One of the outstanding symptoms, if not the chief symptom, in our patients, was the respiratory difficulty, which was variously described as dyspnea, stertorous breathing, and Cheyne-Stokes respiration. In one, the respiratory difficulty was so marked that the presence of a foreign body in the trachea was considered. The respiratory difficulty was always accompanied by cyanosis.

The cerebrospinal fluid removed from the 3 patients who lived long enough to allow a spinal puncture to be done, was clear, colorless, and under increased pressure. One specimen of cerebrospinal fluid contained no cells, another 5 white blood cells and still another contained 11, 2 being within normal limits and 1 only slightly increased. The fluid in 2 cases contained many red blood cells. The question arises as to whether or not the presence of the red blood cells is of any significance. If it were possible to exclude the factor of trauma, the presence of the red blood cells would be important and would speak for hemorrhagic encephalitis, However, it is possible that the red blood cells were due to trauma caused by the spinal puncture, for no matter how clear the cerebrospinal fluid, it is still possible that there was some trauma to the venous plexus of the cord. One must therefore attach no diagnostic importance to the presence of red blood cells in the fluid, although, as stated, they may be significant. There was no increase in globulin in the cerebrospinal fluid in any of the three specimens. In one, the cerebrospinal fluid sugar was increased, judging by the fact that the method used for the determination was the one described by Somogyi,[1] by which non-meningitic and encephalitic fluid usually contains 80 mg. sugar or less per 100 cc. (Cohn, Levinson and McCarthy).[2] Yet the increase was only slight (5 mg.+) and therefore no diagnostic conclusions could be drawn from the cerebrospinal fluid sugar in this case.

The results of the cerebrospinal fluid examination of these 3 patients corroborates the previous statement by one of us (Levinson)[3] that there is no uniformity in the cerebrospinal fluid changes

in encephalitis. It is thus possible that in instances of encephalitis there may be marked cerebrospinal fluid changes, moderate changes or no changes whatsoever.

We believe that the cerebrospinal fluid changes depend upon the meningeal involvement; the greater the meningeal involvement, the more pronounced the cerebrospinal fluid changes.

Of great interest to us was Case 5, in which the encephalitis which caused the patient's death was apparently superimposed on an old encephalitis. The increase in glia cells and capillaries, the alteration of the nerve fibers and myelin sheaths, the presence of blood pigment and lymphocytes, were characteristic (McAlpine).[4]

It may be of interest to note that after the histologic examination in Case 5 was completed, and after the changes characteristic of an old encephalitis were found, the relatives were asked for further information. It was then learned that in 1917 the patient had suffered an attack of influenza. No definite information as to a possible encephalitis at that time could be obtained, but it had been noted that since that time his facial expression had gradually changed and had become mask-like. His movements had gradually become slower.

The simultaneous occurrence of recent and old encephalitis has been observed by us in another instance. It is a matter of speculation whether the old encephalitis had caused a local lack of resistance favoring the recent encephalitis—either mechanically or immunologically—or whether the presence of the old and recent encephalitis in the same brain was a coincidental occurrence.

The presence of Gram-positive diplococci in the brain in this case is noteworthy. Economo[5] and v. Wiesner[6] believed that a diplo-streptococcus is the causative agent of lethargic encephalitis. There is, however, no evidence that the bacteria had caused the encephalitis in our case, particularly because they were found pricipally in the bloodvessels. Zinsser[7] says that "logic forces one at the present time to reject the bacterial causation of this disease (epidemic encephalitis)."

It is interesting that bronchopneumonia was found at autopsy in the 4 instances in which the lungs could be examined. Clinically, evidence of bronchopneumonia was present in only 1 instance. The recognition of bronchopneumonia may have been more difficult, first, because the area involved was small, and second, because the symptoms were masked by the encephalitis. In Case 5, the bronchopneumonia was at least 3 or 4 days old and yet the patient, who was a physician, did not complain of being sick. It is possible that the respiratory tract was the portal of entry for the causative agent of the encephalitis.

Histologically, these 5 cases may be classified into two groups. The outstanding features in the first 3 brains were the extravasation of red blood corpuscles in addition to the infiltration of lympho-

cytes and a few neutrophils. It is known that the extravasation of red blood corpuscles may occur in cases of general intoxication, constitutional disturbances, etc. (Hassin)[8] However, in addition to the red blood corpuscles, other cellular elements were found in the perivascular spaces in sufficient numbers to warrant the diagnosis of encephalitis. The extravasation of red blood corpuscles is one of the earliest histologic findings in these cases. This is borne out by the fact that, as far as can be determined from the clinical history, the duration of the disease in our patients was extremely short. In the last 2 brains, a larger number of neutrophils was present. However, red blood cells and lymphocytes were also found free in the tissue in these 2 cases. In his study of lethargic encephalitis, Economo[5] described minute accumulations of neutrophils, without destruction of the brain tissue in addition to red cells and lymphocytes, in only 1 case, while neutrophils were absent in the other case.

The rapid occurrence of death of the 5 patients is striking. If an autopsy had not been performed in the first case, it probably would have gone on record as death "due to the ingestion of a foreign body." In other words, it must be realized that fulminating encephalitis may be the cause of sudden, unexpected death. It may be mentioned in this connection that Kolisko,[9] in his comprehensive monograph on "Sudden Death from Natural Causes," does not mention encephalitis as a cause of sudden death.

In view of the enlarged thymus in the first child and of the marked hyperplasia of the lymphadenoid structures in the first 3 patients, it should be decided whether or not these children should be classified as having status thymolymphaticus and whether or not the suddenness of the onset of the disease and death can be linked with status thymolymphaticus. There is still much discussion as to whether or not this status can be linked with a general lowered resistance of the tissue. Ever since the report of the British Commission on this question (Young and Turnbull)[10], the assumption of status thymolymphaticus has fallen into discredit. And yet, in doing routine autopsy examinations, one comes across a rare instance of the sudden death of an individual who had a large thymus and generalized hyperplasia of the lymphadenoid structures. Death in such a case may have followed an insignificant trauma. If such a case reveals at autopsy the absence of inflammatory lesions which *per se* might have been responsible for the hyperplasia of the lymph nodes, we believe that the assumption of a status thymolymphaticus is still justified, at least because it provides a morphologic explanation for the sudden and unexpected death. In the first 2 cases of encephalitis, the duration of the disease was so short that we cannot believe that the acute inflammation had caused the general lymphoid hyperplasia. In our opinion, the rapidity of the course of the disease and death of these children may be explained

by the assumption of a general lowered resistance which had its morphologic equivalent in the enlargement of the lymphadenoid structures throughout the body. In the third patient with encephalitis, however, the inflammatory changes were marked and this alone may explain the hyperplasia of the lymphadenoid tissue. In other words, the suddenness of the deaths of some of the patients reported here cannot, in our opinion, be explained on the basis of a status thymolymphaticus, but must be regarded solely as the result of the fulminating encephalitis.

Various types of encephalitis have been described in the literature. Some authors stress the epidemic occurrence (epidemic encephalitis), some emphasize the particular symptoms (lethargic encephalitis), while others point to characteristic gross or histologic findings (hemorrhagic encephalitis, etc.). Neither clinically nor morphologically can we be absolutely certain as to which group of encephalitis our cases belong. The redness of the brain and the predominance of the hemorrhagic exudate which were found in every instance justify the anatomic term "acute hemorrhagic encephalitis." It may be stressed that this disease had occurred sporadically and there was not a single instance where it was transmitted to anyone who came in contact with the patient. As stated before, the outstanding clinical feature common to all 5 of our cases of encephalitis was the rapidity of its course and of the death of the patients. This was so striking to us that we believe that the term "pernicious" or "fulminating" encephalitis is justified to describe fully the most outstanding clinical picture.

The diagnosis of encephalitis is always difficult, since the disease must be differentiated from other acute infections of the central nervous system, particularly from tuberculous meningitis, brain abscess and brain tumor, and from what is commonly called meningism. However, fulminating encephalitis, as we have here described it, presents the further difficulty in that it must be differentiated from conditions which lead to sudden death and which do not involve the central nervous system, such as foreign bodies in the lungs, and circulatory collapse.

Summary and Conclusions. Fulminating hemorrhagic encephalitis is characterized by sudden onset, great respiratory difficulty, coma, and rapid death. The course of the disease is very short and death may sometimes be sudden. The cerebrospinal fluid may be hemorrhagic, but is usually clear. It may have an increase in cells, or may show no changes. The greater the meningeal involvement, the more pronounced the cerebrospinal fluid changes. Histologically, the brain reveals a predominance of a hemorrhagic exudate in addition to perivascularly arranged lymphocytes and neutrophils. In one instance, fulminating hemorrhagic encephalitis was found superimposed on an old encephalitis. In children, a generalized enlargement of the lymphadenoid apparatus is usually present. The

sudden death due to fulminating hemorrhagic encephlitis may be regarded as an example of "sudden death from natural causes," in Kolisko's definition of the term.

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CARBOHYDRATE METABOLISM IN HUMAN HYPOTHYROIDISM INDUCED BY TOTAL THYROIDECTOMY.

III. A Case of Diabetes Mellitus Treated by Total Ablation of the Normal Thyroid Gland.*

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For several years it has been recognized that diabetes mellitus is aggravated by thyrotoxicosis and benefited by myxedema.

Many investigators, including Fitz,[1] Wilder,[2] John,[3] Joslin and Lahey,[4] and Andersen[5] have observed that the diabetic condition

* The first and second papers of this series appeared in this Journal, **188**, 790 and 796, 1934.

of patients with diabetes and thyrotoxicosis was alleviated markedly after subtotal thyroidectomy. Similarly, others have reported amelioration of diabetes associated with thyrotoxicosis, following iodin treatment[6,7] and following Roentgen[8] therapy.

Rohdenburg,[9] and Weinstein[10] observed patients in whom all clinical evidences of diabetes disappeared as myxedema spontaneously developed. Wilder[2] also has reported a case in which the carbohydrate tolerance increased markedly when spontaneous myxedema developed. Weinstein[10] found that the evidences of diabetes reappeared in his patient when the basal metabolism was brought again to normal by thyroid. Other investigators also have found that the diabetic condition became aggravated when patients with diabetes and myxedema were given thyroid[2,5,10–14] and that when thyroid medication was discontinued in these patients, diabetes again became less severe.[2,11,12,13]

These striking clinical indications that a lowering of thyroid activity benefits diabetes led us in November, 1933, to consider treating a patient with uncontrollable diabetes and incipient tuberculosis by the induction of hypothyroidism through total ablation of the thyroid gland. The patient had mitral stenosis and sufficiency but had never experienced any symptoms nor shown any signs of congestive failure. This patient had no evidences of thyrotoxicosis and the basal metabolic rate averaged +7%. The usual methods of treatment had failed to control her diabetes. It was hoped that by producing hypothyroidism the diabetes might be alleviated and the progress of the tuberculosis be retarded indirectly. In previous studies of the control of hypothyroidism after total thyroidectomy in patients with chronic heart disease, it had been found that a basal metabolic rate of approximately −25% to −30% could be maintained without discomfort to the patient.[15,16] Total ablation of the thyroid gland according to the technique of Berlin[17] was therefore performed in this patient after a thorough explanation of the situation to her.

Case Report. On May 16, 1931, Mildred D. (B. I. H. Case 10811) a 22-year-old, American-born, Jewish housewife, entered the Beth Israel Hospital complaining of marked loss of weight for 4 months, and polydipsia, polyuria, and polyphagia for 1 month. The family history was negative; the past history was essentially negative except for the presence of a cardiac murmur since the age of 12, at which time she had had a severe attack of chorea. The urine at the time of admission showed complete reduction for sugar and 4+ acetone. The fasting blood sugar was 192 mg. per 100 cc.* The body height was 62 inches and the weight 110 pounds. The B. M. R. was −13%. Hematological studies revealed normal findings. The patient remained in the hospital 13 days during which time the diabetes was controlled by a diet consisting of 110 gm. of carbohydrate, 50 gm. of protein, and

* Blood sugar measurements were made by the method of Folin.[18] Plasma cholesterol measurements by the method of Bloor[19] and basal metabolic rates using a Collins-Benedict-Roth spirometer and calculating according to the normal standards of Aub and Dubois.[20]

70 gm. of fat (1270 calories), and 10 units of insulin daily. She was discharged to the Diabetic Clinic of the Out Patient Department on this same régime. Because of loss of weight during the next 2 months, her diet was gradually increased to 180 gm. of carbohydrate, 80 gm. of protein, and 140 gm. of fat (2300 calories), and the insulin to 20 units daily.

In February, 1932, the patient returned to the Clinic after an absence of 6 months, during which time she had had a therapeutic abortion and had not adhered to her dietary and insulin routine. At this time her diabetes was so severe that 66 units of insulin daily, divided in three doses, were required.

In June, 1932, she was admitted into the wards with signs of subacute appendicitis. An appendectomy was performed. The operation and convalescence were uneventful. She remained in the hospital 55 days, during which time it was extremely difficult to control the diabetes adequately. The fasting blood sugar values were repeatedly approximately 350 mg. per 100 cc., the insulin dosage from 40 to 80 units daily. During the next 15 months the patient returned to the Diabetic Clinic every 1 to 2 weeks. Many dietary and insulin adjustments were attempted. She was finally regulated on a diet of carbohydrate 130 gm., protein 80 gm., fat 120 gm., totalling 1900 calories, and 66 units of insulin divided in three doses daily. On this régime she did fairly well for about a year, although sugar was still repeatedly found in the 24-hour urine, and changes from insulin reactions at one time of the day, to gross glycosuria at other times were frequent.

On October 23, 1933, because of the steadily increasing severity of her diabetes, and the development of lung lesions she was readmitted to the hospital. Her weight at this time was 112 pounds. She complained of general weakness. Examination of the lungs revealed dullness, increased transmission of breath sounds, and occasional crepitant râles over the right apex. Stereoroentgenographic examination of the lungs revealed an area of increased density at the right apex, the central portion of which contained an ovoid area of diminished density, suggesting early cavitation. There was no cough, hemoptysis, or night sweats, the temperature was normal, but the pulse rate ranged between 80 and 100. A diagnosis of pulmonary tuberculosis was made. The patient also had mitral stenosis but had at no time experienced signs or symptoms of heart failure, nor had her activities been limited by the cardiac condition.

During the 2 weeks between October 23 and November 6, 1933, in the hospital, she was maintained at complete bed rest. On a diet of 140 gm. of carbohydrate, 80 gm. of protein, and 140 gm. of fat (2140 calories), she required as much as 105 units of insulin daily divided in four doses. In spite of this, her diabetes remained uncontrolled. The blood sugars varied from very high to very low figures during the same day in spite of adjustments in insulin and diet.

The treatment of this patient with severe diabetes and tuberculosis of the lungs was an extremely difficult problem. She obviously required meticulous supervision of her diabetes and bed rest for her tuberculosis. Financial and social circumstances prevented her from receiving adequate treatment at home. The diabetic condition was intractable under the optimum conditions in the hospital and so it was deemed unwise to submit her to the less closely supervised régime of the average sanatorium.

On November 6, 1933, total ablation of the thyroid gland was performed, in the hope that hypothyroidism might alleviate the diabetes and thereby also have a favorable effect upon the tuberculosis. The postoperative course was uneventful. On pathologic examination the thyroid gland was found to be normal. The patient remained in the hospital under close observation for 5 months.

The average basal metabolic rate before operation was +7%; the body

weight 111 pounds (Chart I). During the 5 postoperative months the patient was confined to bed, because of the tuberculosis, and given the same diet as that just prior to operation, namely: 140 gm. of carbohydrate, 80 gm. of protein, and 140 gm. of fat (2140 calories). Following operation, the B. M. R. decreased gradually, and at the same time the insulin requirements also decreased (Chart I). Failure to decrease the amount of insulin occasionally resulted in mild insulin reactions. The B. M. R. 45 days after operation had decreased to −30% and the insulin requirement to 35 units daily. The body weight had increased to 118 pounds. From the 50th to the 82d postoperative days the basal metabolic rate ranged between −30% to −35% and the insulin requirements varied from 35 to 50 units daily. The plasma cholesterol concentration was high (Table 1). By the 82d postoperative day her body weight had increased to 127 pounds. Beginning approximately 2 months after operation, the patient experienced some weakness and drowsiness. These symptoms became gradually more severe so that beginning on the 82d postoperative day she was given small amounts of desiccated thyroid (gr. $\frac{1}{4}$ daily, Armour). During the 10 days on this medi-

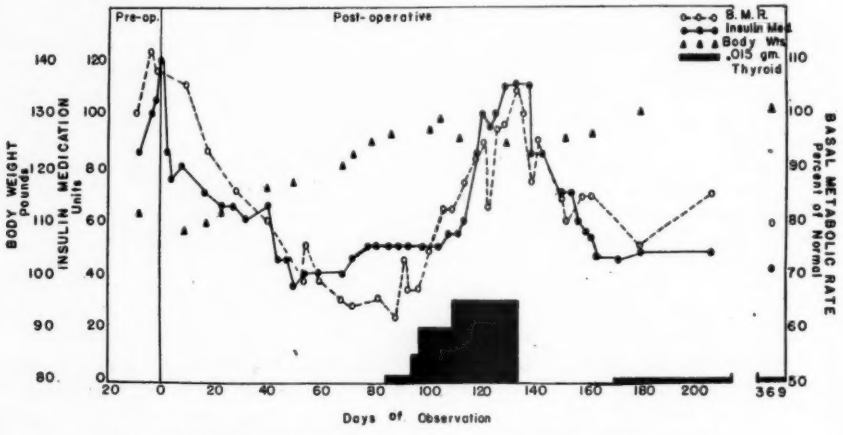

CHART I.—Effect of total thyroidectomy on insulin requirement.

cation the B. M. R. increased from its lowest value of −38% to approximately −30%; the insulin dosage remained 50 units daily (Chart I). The symptoms of myxedema were relieved.

In order to determine whether the postoperative decrease in insulin requirement of this patient was due to the development of hypothyroidism, or to some other factor, sufficient thyroid was administered to raise the metabolism to the pre-operative level. The thyroid medication was increased gradually, and 135 days after operation the B. M. R. had increased to +5% (Chart I), and the serum cholesterol had decreased to normal (Table 1). The patient now presented the same intractable diabetes as before operation; 110 units of insulin daily again were required (Chart I).

Thyroid medication was omitted and the B. M. R. and insulin requirements again decreased (Chart I).

On April 15, 1934, 5 months after operation, she was discharged to the Diabetic Clinic of the Out Patient Department with practically the same diet (carbohydrate 140 gm., protein 80 gm., fat 120 gm., totalling 1960 calories) as that employed throughout the study, and 46 units of insulin daily divided in three doses. Her B. M. R. at this time was −20%. She was allowed up

and about and to do light work. On May 3, with the B. M. R. at −24%, and 46 units of insulin daily divided in two doses some weakness was again experienced so that thyroid grains $\frac{1}{10}$ daily were prescribed.

TABLE 1.—EFFECT OF TOTAL THYROIDECTOMY ON THE BASAL METABOLISM, PLASMA CHOLESTEROL AND INSULIN REQUIREMENT.

Date.	Basal metabolic rate, % deviation from normal.	Plasma cholesterol, mg. per 100 cc.	Insulin units.	Daily thyroid medication, gm.
Oct. 25, 1933	+ 2	...	95	
Nov. 2, 1933	+12	...	100	
Nov. 5, 1933	+ 8	...	105	
Nov. 6, 1933	Total ablation of normal thyroid gland.			
Dec. 1, 1933	−14	...	65	
Dec. 16, 1933	−20	...	55	
Dec. 26, 1933	−32	520	45	
Jan. 13, 1934	−35	694	40	
Jan. 31, 1934	−34	...	50	.015
Feb. 15, 1934	−26	510	50*	.120
Feb. 24, 1934	−13	208	60*	.180
March 10, 1934	− 3	189	100	.300
March 18, 1934	+ 5	166	110*	.300
March 24, 1934	−13	245	85*	
May 3, 1934	−24	...	48	
May 29, 1934	−15	463	48	.007
Aug. 30, 1934	−17	284	48	.007
Nov. 10, 1934	−21	390	42	.007

* Indicates that the urine showed sugar during the entire 24 hours and that more insulin was required.

From May 1934 to November, 1934 the same diet prescribed on discharge from the hospital was given. Between 42 and 48 units of insulin daily proved sufficient to control the diabetic condition. Because of financial difficulties, the patient did not follow the dietary régime on a few occasions and glycosuria occurred. On one of these occasions she was admitted to the wards for proper regulation and was discharged in 10 days on the same diet and the same amount of insulin on which she was stabilized before, namely, 44 units daily divided in two doses. With the exception of these few occasions, the urine has been sugar-free most of the day. The body weight has been approximately 130 pounds. Her B. M. R. has remained approximately −20%. Except for a short period when she complained of cramps in the calves of the legs and occasionally in the feet, she has been free from symptoms of myxedema, receiving thyroid grains $\frac{1}{10}$ daily.

It is interesting to note that for several months following thyroidectomy, she had difficulty in recognizing insulin reactions,[21] the only symptom being that of precordial or epigastric weakness. Beginning October, 1934, the characteristic symptoms of sweating and inward trembling sensation have returned.

The pulmonary process in this patient has become arrested. On March 23, five months after operation, Dr. Mark Joress of the Pulmonary Clinic made the following observation: "A summary of symptomatology, physical examination and radiographic findings warrants, I believe, the opinion that the tuberculosis is showing a constant regression." On examination 6, 9 and 12 months after operation, no clinical or Roentgen ray signs of

activity in the lungs could be found. On November 1, the Roentgen ray report states "re-examination of the chest shows the areas of increased density in the upper portion of the right lung field still present, but there are no progressive changes in the lungs."

Since this paper has been in press the patient has maintained her clinical improvement. On May 9, 1935, she was found to require 40 units of insulin daily. The midday blood-sugar concentration was 124% mg., the serum cholesterol was 328% mg., and the urine specimens during the entire 24 hours were sugar-free.

Discussion. The therapeutic results obtained by total thyroidectomy in this patient have been gratifying up to this time, 1 year after operation. On an adequate diet her diabetes has been controlled with 42 to 46 units of insulin daily, divided in two doses, while prior to the operation her diabetes could not be controlled adequately even with 85 fo 105 units daily. The tuberculosis has been arrested by 5 months of bed rest following operation and probably also in some measure through the alleviation of her diabetic condition. At the level of hypothyroidism (B. M. R. of approximately −20%) maintained in this patient by the administration of small doses of thyroid (Armour's gr. $\frac{1}{10}$ daily), she suffers no appreciable discomforts. She now leads a happy and useful life, taking care of her home for her family. She looks more healthful than before operation, partly because of the gain in weight. Her general appearance is in no manner that of a patient with myxedema.

Observations of the effect of total thyroidectomy on the carbohydrate metabolism of experimental diabetes in animals have been discussed in the second paper of this series.[22] O'Day, in 1915,[23,24] removed the "greater portion" of the thyroid gland in 2 young patients with diabetes and no evidence of thyroid disease. During the first few postoperative months these subjects showed a marked increase in tolerance,[23] but subsequently both patients died in diabetic coma.[24] In view of the fact that maximal subtotal thyroidectomy may cause only temporary hypothyroidism,[25] it seems possible that permanent hypothyroidism was not effected in O'Day's cases with diabetes. Crile,[26,27] also in 1915, performed section of the cervical sympathetic, left suprarenalectomy and partial thyroidectomy in a patient with diabetes. While satisfied with the results obtained in this patient, Crile was unwilling to ascribe the improvement entirely to the operation because the Allen treatment was employed at the same time.[27]

A few weeks after our patient was operated upon, Wilder, Foster and Pemberton[28] reported a case of severe uncomplicated diabetes and no thyroid disease in which radical thyroidectomy was done on May 30, 1933. The development of hypothyroidism was accompanied by a marked increase in sugar tolerance which paralleled roughly the decrease in the B. M. R. One year after operation, the patient required 15 units of insulin daily at a level of hypo-

thyroidism compatible with freedom from discomforts of myxedema, whereas prior to operation he had required approximately 30 units daily.[28,29]

The improvement of the diabetes in Wilder's patient and in our patient after the development of induced hypothyroidism is in accord with the improvement in diabetes which has been observed to attend the development of spontaneous myxedema.[2,9,10] That the diabetes in our patient again returned to its pre-operative severity when the B. M. R. was raised to its pre-operative level by thyroid medication (Chart I), is in accord with the finding that diabetes is rendered more severe when the basal metabolism is increased by thyroid medication[2,5,10–14] or by thyroid disease.[1–5] The improvement in the diabetes of our patient was not related to subsidence of the tuberculosis, for raising the metabolic rate by thyroid to the pre-operative level again reproduced the severe diabetic state witnessed before operation.

In order to remain free from the discomforts of myxedema our patient requires grains $\frac{1}{10}$ of thyroid (Armour's) daily. On this thyroid dosage a hypothyroid state is maintained with a level of basal metabolism of approximately -20%. This principle of maintaining a hypothyroid patient at a level of metabolism just sufficiently high to avoid the severe symptoms of myxedema should be applicable likewise in those patients with spontaneous myxedema and diabetes whose diabetes becomes severe when the basal metabolism is brought to normal by thyroid.

The elevated blood cholesterol values found at intervals after total thyroidectomy (Table 1) in this patient were related, apparently, to the degree of hypothyroidism rather than to the diabetic state. Very high cholesterol values were obtained during the third post-operative month when the B. M. R. was very low and the patient was experiencing distressing symptoms of myxedema such as weakness and drowsiness. This is in accord with previous observations following total thyroidectomy in patients with chronic heart disease.[30] When the B. M. R. was returned to normal by thyroid medication, the concentration of serum cholesterol became normal, subsequently increasing again as the B. M. R. decreased following reduction in thyroid medication (Table 1).

The mechanism through which diabetes is benefited by hypothyroidism is not entirely understood. In the first communication of this series[31] it was pointed out that in non-diabetic patients, hypothyroidism induced by total thyroidectomy had but little effect on the glucose tolerance curve and the concentration of the sugar of the serum after a fast. On the other hand the carbohydrate tolerance of a patient with mild diabetes, in whom total ablation of the normal thyroid gland was performed for the relief of angina pectoris, increased considerably after hypothyroidism developed.[31] The glucose tolerance curve also became considerably more like

normal when hypothyroidism developed after total thyroidectomy in a patient who before operation had mild hyperthyroidism and an abnormal glucose tolerance curve.[31] In the second communication of this series,[22] it was shown that the effect of the subcutaneous injection of 20 units of insulin on the blood sugar of non-diabetic patients was the same before and after the development of hypothyroidism; in 6 patients 20 units of insulin caused an average maximum decrease of 34% in the blood sugar before operation and the same average decrease after hypothyroidism developed. Fitz[1] has suggested that a lowering of the B. M. R. affords improvement in patients with diabetes. Wilder[28,29] accounts for the improvement in diabetes, which accompanies the lowered B. M. R. in hypothyroidism, by an increased sensitivity to insulin. Joslin,[32] before the insulin era, found that the metabolism in diabetes was greatly influenced by high and low diets.

Although maximal subtotal removal of the normal thyroid gland in man occasionally may produce permanent hypothyroidism,[25,29] evidence has been presented[25,33] that total removal of the normal thyroid gland must be performed in order to insure permanent hypothyroidism in every instance. In 2 patients with heart disease in whom maximal subtotal removal of the normal thyroid gland was performed at the Beth Israel Hospital[25] hypothyroidism did not persist. Other investigators have reported similar experiences.[34,35]

Means and Herman[36] have described the rate of decrease in B. M. R. following the abrupt cessation of thyroid medication in patients with myxedema. From the B. M. R. studies in our patient it is evident that the rate of decrease of metabolism is approximately the same following total ablation of the normal thyroid gland and cessation of thyroid medication which has restored the B. M. R. to normal (Chart I). The rate of decay of thyroid activity, both after total thyroidectomy and after thyroid medication in this patient accords with the findings of Means and Herman.[36]

The severity of the diabetes in our patient, together with the complication of tuberculosis, appeared to justify the attempt to benefit her by inducing hypothyroidism through total ablation of the normal thyroid gland. This procedure obviously is not applicable to the treatment of diabetes mellitus unless the case is of marked severity and uncontrollable by the usual therapeutic measures. Wilder and his associates[29] concluded from their study of the effect of hypothyroidism induced by radical thyroidectomy in a patient with diabetes that "the remedial result was not sufficient to justify recommending the procedure as a treatment." It should be noted that their patient on an adequate diet required only 30 units of insulin daily before hypothyroidism was induced. From the results in our case of severe diabetes we feel that unusual patients with diabetes of similar severity and unstable character may benefit from total thyroidectomy.

Summary. 1. A patient with severe uncontrollable diabetes mellitus complicated by tuberculosis of the lungs was treated by total ablation of the thyroid gland. Before operation, the B. M. R. was +7% and the patient showed no evidences of hyperthyroidism. The extirpated thyroid tissue was found normal on gross and microscopic examination.

2. The diabetic condition which could not be adequately controlled prior to operation under optimal conditions with diet and an average insulin dosage of 95 units daily was readily controlled by diet and 44 units of insulin daily after hypothyroidism developed.

3. A level of hypothyroidism at which the patient remained free from any unpleasant symptoms of myxedema was maintained by very small doses of thyroid.

4. It is suggested that the treatment of hypothyroidism with very small doses of thyroid as applied in this patient may be useful also in some patients with diabetes and spontaneous myxedema.

5. As evidence that the reduction in insulin requirements in our patient was due to the hypothyroid state, it was found that administration of thyroid sufficient to restore the pre-operative metabolic level resulted in relapse of the patient's diabetic condition to the pre-operative status.

6. Total thyroidectomy is not advised in the treatment of diabetes mellitus except in the rare case with very severe diabetes which cannot be controlled adequately by the application of all known therapeutic measures.

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(Titles have been omitted for sake of brevity.)

THE VARIABLE AUSCULTATORY SIGNS OF PULMONARY CAVITIES.*

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Most of the pulmonary cavities, irrespective of whether they are tuberculous, bronchiectatic, acute suppurative, or neoplastic in origin, do not reveal their presence by cavernous breath sounds. In 350 cases of pulmonary cavities which I have studied at the Sea View, Cumberland, and New York Post-Graduate Hospitals, I found that 246 lack most if not all of the classic auscultatory signs of cavitation. However, I want to stress from the start that these findings in no way disparage the diagnostic importance of the stethoscope, but merely point to the necessity of revising the hitherto accepted physical signs of cavities and their probable mechanism. Whereas pectoriloquy and amphoric breathing may be heard over an old fibroid lesion which is of little clinical significance, very scanty signs may be elicited over an active pulmonary cavity which requires immediate therapeutic attention. Of the 246 cases which lacked cavernous breathing, 36 revealed no inkling of the presence of any pulmonary lesion, but the rest of the cases manifested certain adventitious signs which when systematized properly proved helpful in the diagnosis of cavities.

The 350 cases of pulmonary cavities which I have studied, may be divided into four groups as far as auscultatory signs are concerned: *a*, Cavities which manifest themselves through the classic cavernous signs; *b*, cavities over which no suspicious signs of any pulmonary

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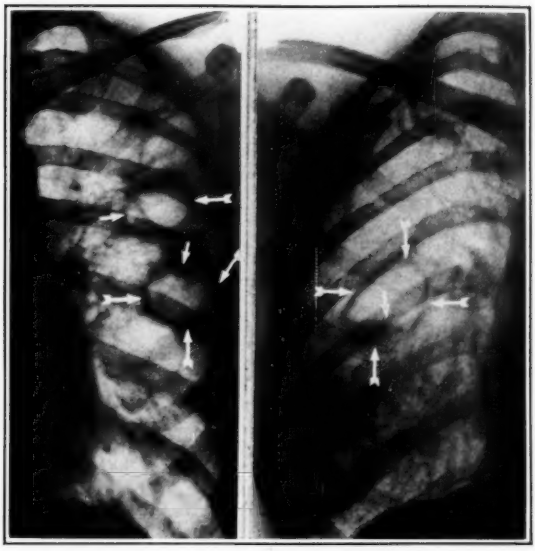
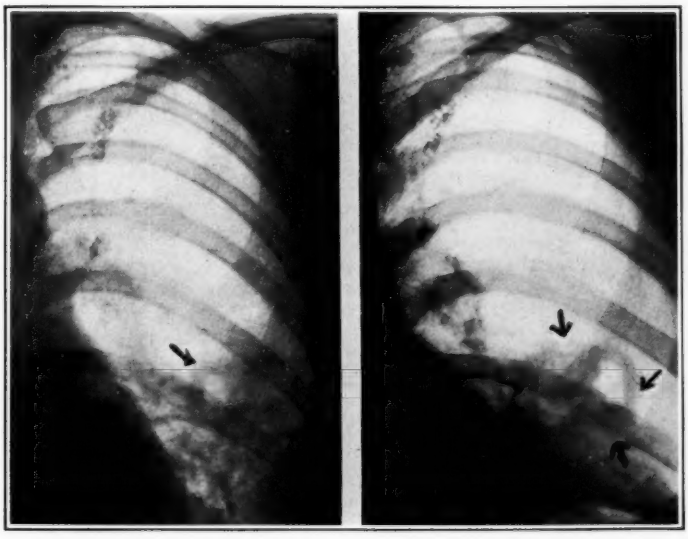


A *B*

FIG. 1.—*A*, Two adjacent small cavities in outer zone of left pulmonic field. The only adventitious sign elicited over this area was coarse râles after cough. *B*, Cavity in midzone of right pulmonic field (note fluid level). Altered breath sounds and moist inspiratory râles were limited to this area anteriorly, but no adventitious signs were elicited posteriorly.



A *B*

FIG. 2.—*A*, Caseous lesion in left lower lobe, but no definite cavity is outlined on the roentgenogram. Auscultation revealed modified breath sounds and crepitant râles on ordinary inspiration, limited to same area anteriorly and posteriorly. *B*, A roentgenogram of the same case after induction of left artificial pneumothorax. Note the well-outlined cavity and its thick capsule.

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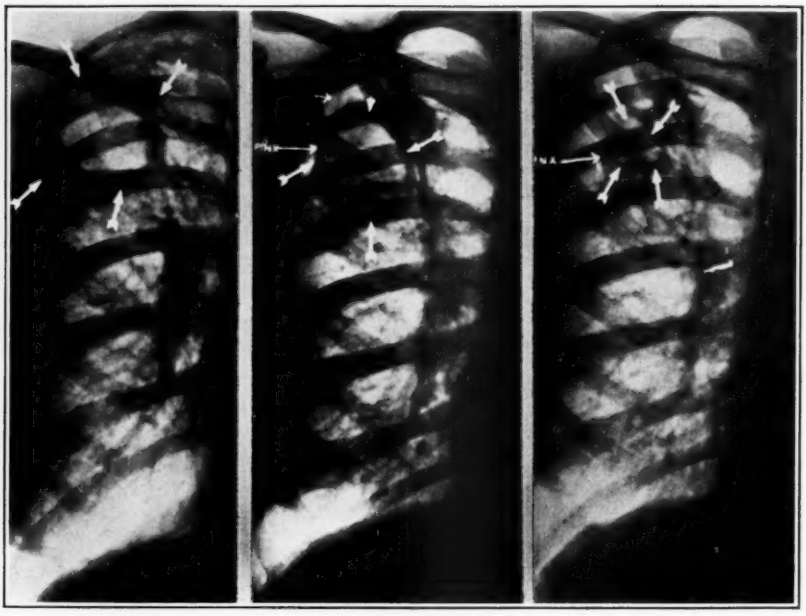
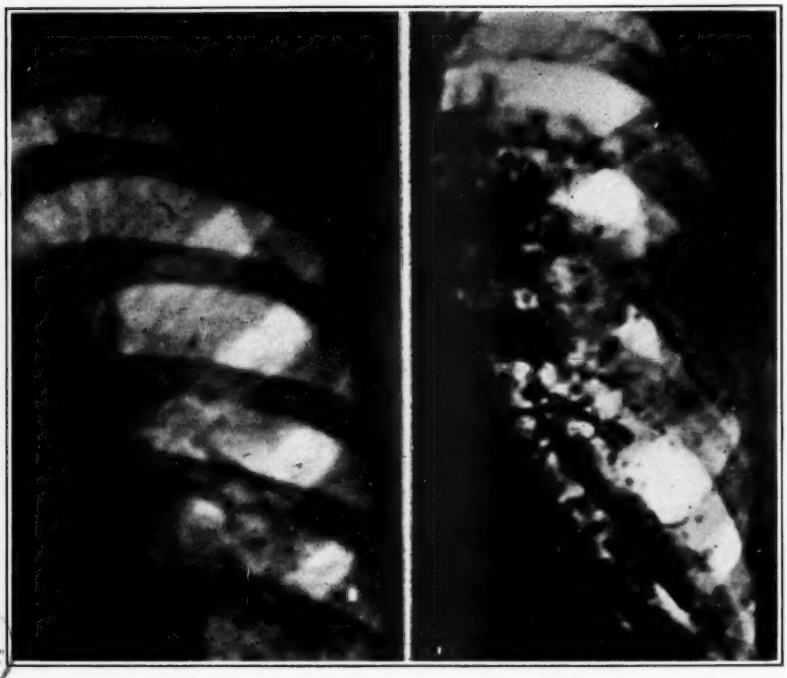


A *B* *C*

FIG. 3.—*A*, A large cavity in right upper lobe with all the classic cavernous signs. *B*, Same case after injection of 300 cc. of air into pleural cavity; only altered breath sounds and coarse inspiratory râles are now heard over subclavicular fossa. *C*, A roentgenogram a few weeks later shows cavity reduced in size; cough and deep breathing elicit only a few râles over area of cavitation.



A *B*

FIG. 4.—*A*, No definite lesion is visible, though cavernous breathing was heard over left lower lobe. *B*, Same case after bronchography, revealing 2 bronchiectatic cavities communicating by a small narrow canal.

lesion can be elicited; these I named absolutely mute; *c*, relatively silent, *i. e.*, such cavities which do not exhibit any of the classic signs but over which other adventitious sounds are heard, such as altered breath sounds, modified whispered voice, inspiratory râles over a limited area, etc.; *d*, intermediate, *i. e.*, such cavities which at times are absolutely silent and at other times reveal themselves by certain adventitious stethoscopic signs, thus belonging alternately to Groups *b* and *c*.

The following table indicates the order of frequency of the four groups of cavities:

TABLE 1.—FREQUENCY OF 4 TYPES OF CAVITIES.

	No. of cases.	Frequency, %.
Total number	350	
Relatively silent cavities	177	50.6
Cavities with cavernous breathing	104	29.7
Intermediate cavities	36	10.3
Absolutely mute cavities	33	9.4

It is evident from these figures that the relatively silent cavities are by far the most prevalent. Their "silence" applies only to cavernous sounds, otherwise they invarably manifest themselves through certain congeries of stethoscopic signs. The figures also clearly indicate that cavernous breathing, as a diagnostic criterion of a cavity, takes only a second place, for it was present in only about 30% of all cavities. On the other hand, it is of clinical significance to note that a small number of pulmonary cavities cannot in any way be detected by physical signs (33 cases out of a group of 350 cases). If we also add the intermediate cavities to these so-called absolutely mute ones, the total would be increased to 69 cases, which would mean that at most about 20% of all pulmonary cavities could not be detected by physical signs alone. However, in about 80% of all pulmonary cavities the stethoscope was sufficient to diagnose or at least to suggest the presence of a cavity.

The question arises, what are the factors which modify the physical signs of a cavity, and what bearing have they on the clinical course and possible therapeutic procedure to be followed? Without going into a detailed discussion of breath sounds in general, it might be stated that two views prevail: 1, that they are produced in the larynx; 2, that they originate in the chest. Bushnell[1] seems to have proven experimentally that the breath sounds are produced in the larynx, but are modified by conduction and sympathetic vibrations of the lung tissue and thoracic cavity. Chauveau,[2] on the other hand, seems clearly to have established the fact that experimental obliteration of the glottic sound does not annul the inspiratory sound heard by auscultation over the lung. Hence, he believes that it originates in the chest itself. Neither of these views alone can explain the production of cavernous sounds. It is possible

that a laryngeal element is present in all breath sounds, but the inrush of air into the cavity and the sympathetic vibrations set up in its wall are principally instrumental in imparting the blowing cavernous tinge to its respiratory sound. The following factors are to be considered in the mechanism of production of auscultatory signs over a cavity: *a*, the communicating bronchus; *b*, the consistency of the wall or capsule of the cavity; *c*, the topographic relation to the thoracic wall and to the main bronchi; and *d*, the surrounding lung tissue and medium of conduction. The size and shape of the cavity also play a certain rôle in modifying the breath sounds.

The closure of a communicating bronchus may be produced by fibrosis or by secreta and necrosed material. Complete fibrosis of a bronchus is a rare phenomenon, and Dr. Auerbach, the pathologist at Sea View Hospital, tells me that he has seen only 2 cases of complete fibrosed bronchi in about 600 autopsies. However, plugging of the lumen of a bronchus by thick tenacious secretion is more common, particularly in cavities located in the outer zone of the pulmonic field (Fig. 1*A*), the afferent bronchus of which is of small caliber and can be easily obliterated. No auscultatory signs may be heard over such cavities, though coughing may often dislodge the plug and reopen the bronchus with consequent changes in the physical signs.

When the bronchus, communicating with the cavity, is of larger caliber, it will rarely, if ever, become plugged entirely by sputum. The physical signs of such a cavity will vary mostly with its distance from the periphery and the consistency of its walls. Fig. 1*B* shows a medium-sized cavity in the midzone of the third interspace of the right hemithorax. Altered breath sounds, increased whispered voice, and numerous moist râles were heard over this area anteriorly, but no adventitious sounds at all were elicited posteriorly. Stereoroentgenoscopy and Roentgen ray plates taken in the P. A. and A. P. positions, revealed the cavity to be located near the periphery anteriorly. The difference in these physical signs anteriorly and posteriorly is useful in locating the position of the cavity which is of great importance in surgical cases. This was a case of a pulmonary abscess which needed surgical intervention.

Altered breath sound and whispered voice, and particularly coarse inspiratory râles heard over a limited area in the chest, are strongly indicative of a cavity. Such cavities have a patent bronchus through which an ingress and egress of air takes place, but the walls of the cavity are soft, ragged, and not very vibratile; consequently the cavernous pitch is not produced. The capsules of these cavities are very poorly outlined on the roentgenograms, though after induction of pneumothorax, when the secretion and débris had been squeezed out from the cavernum, the walls may stand out conspicuously (Compare Figs. 2*A* and 2*B*). In a previous contribution,[3] I pointed out that such cavities, if they are tuberculous

in origin, have a poorer prognosis than the absolutely mute cavities. Artificial pneumothorax is the treatment of choice of such cavities and the sooner this therapy is initiated the better the prognosis. I find these cavities to be more predominant in the caseous-pneumonic type of the clinical classification of pulmonary tuberculosis by Ornstein, Ulmar and Dittler.[4]

The relationship of the surrounding medium to the change in physical signs was studied in a large group of cases of pulmonary cavities which were treated by artificial pneumothorax. Frequent physical examinations in conjunction with serial Roentgen ray examinations have helped much in interpreting the various physical signs of a cavity. Fig. 3*A* shows a cavity in the right upper lobe which exhibits all the textbook cavernous signs. However, after the injection of 300 cc. of air into the right pleural cavity (Fig. 3*B*), the cavernous breath sounds disappeared, though whispered voice was still increased and coarse râles were heard in the subclavicular region on ordinary inspiration. Fig. *C*, a roentgenogram of the same case a few weeks after the initiation of the treatment, shows the cavity markedly reduced in size; the breath sounds at this time were slightly diminished, but deep inspiration and cough elicited moist râles limited to the area of cavitation. If a selective type of pneumothorax is established, the functioning portions of the lung continue to expand and contract with respiratory phases, and no adventitious signs may be heard. Normal lung tissue surrounding a small cavity may also overshadow all the auscultatory signs of a small cavity, particularly if the lung is emphysematous.

It should be stressed however, that cavernous breathing always indicates a cavity, even if the cavity is not outlined on the ordinary roentgenogram. The following case is illustrative in this respect. Cavernous signs were elicited at the right lower base, but no cavernum was visible on the roentgenogram (4*A*). However, on injecting iodized oil, two bronchiectatic cavities were revealed to be connected by a very small distorted bronchial canal (4*B*). We encountered many instances in which the stethoscope was more informative than the Roentgen ray alone.

The presence of cavernous sounds indicates as a rule, an older cavity with a thickened and well-fibrosed capsule. Such cavities are not always amenable to artificial pneumothorax, and surgical collapse is often the only means of obliterating them. The relatively silent cavities, with soft and yielding walls, can often be successfully compressed with a selective type of pneumothorax, the mechanism of which I discussed fully elsewhere.[5] This type of pneumothorax entails very little respiratory and circulatory changes and causes little discomfort to the patient.

It is needless to say that Roentgen ray examination should be used as a routine diagnostic procedure in any suspicious case of respiratory involvement, for it always adds to our clinical under-

standing of the case. Cough or expectoration may not necessarily be complained of even in the presence of a cavity. The scope of this paper does not allow me to discuss fully the cough-reflex and expulsive mechanism of the bronchi and the reader is referred to another contribution.[6] Suffice it to mention here that even a large bronchiectatic cavity may exist without any bronchorrhea, or tuberculous cavities situated at a distance from the main bronchi may cause no cough or expectoration. Such peripheral cavities are, as a rule, of the absolutely mute or intermediate type, for they communicate with bronchi or bronchioles of very small caliber, and may sometimes close or heal spontaneously. Serial Roentgen ray and physical examinations are essential for the determination of the proper therapeutic procedure to be carried out.

Summary. Pulmonary cavities can be divided into four groups as far as auscultatory signs are concerned. Of 350 cases of pulmonary cavities, only 104 (29.7%) exhibited cavernous breathing; 33 (9.4%) gave no inkling whatsoever as to the presence of a pulmonary lesion; 177 (50.6%) lacked the cavernous sound but manifested their presence through other adventitious signs, and 36 (10.3%) were intermediate, *i. e.*, at times were absolutely silent to auscultation and at other times revealed themselves by certain stethoscopic signs.

The factors of primary importance in the production of the variable signs of cavities are: the communicating bronchi, the consistency of the capsule of the cavity, the topographic relations, the surrounding lung tissue and medium of conduction.

The most significant and common signs of early cavitation are modified breath sounds and *localized* coarse râles heard on ordinary inspiration. Such cavities have, as a rule, soft and yielding walls which are easily amenable to collapse therapy. Cavernous breathing generally indicates an older cavity, be it tuberculous or nontuberculous with fibrosed, rigid walls which render it refractory to medical treatment; only radical surgery is able to close completely such a cavity. The absolutely mute cavities can be diagnosed only by roentgenology; they are the least frequent and usually have a fair prognosis.

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PNEUMONIAS DUE TO PNEUMOCOCCUS TYPE VIII.*

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With the introduction of type specific therapeutic sera it has become desirable to classify the pneumococcus pneumonias in accordance with the etiologic type and, if possible, to differentiate them clinically.

The separation of the pneumococci into specific types ultimately depends on the production of type specific antibodies as the result of their reaction with certain animal hosts. It is not unreasonable to suppose that there may be other differences in the manner in which the body responds to invasion by pneumococci of various types.

Specific differences due to the pneumococcus may exist in respect to invasion, course, symptoms and physical signs. It is our purpose to describe the reactions of the body to Pneumococcus Type VIII. Our studies only permit us to sketch the disease picture; details must await more extended observations. At first many cases of Type VIII were included with Type III and unless care is taken they may still be thus designated. Finland and Sutliff[1] have already furnished some data contrasting Types III and VIII in their very valuable contribution.

Frequency. We base our description chiefly on 122 cases in adults (constituting 5.9% of 2067 pneumococcus pneumonias) and 11 cases in children (constituting 2.2% of 500 pneumococcus pneumonias studied on the Pediatric Service of Dr. M. Gleich. The cases were observed during a 5-year period, July 1, 1928, to June 30, 1933. Since then we have observed more than 60 cases among adults on our Adult Service, a few on the Children's Service and several in private practice. The number of admissions to our service due to this disease has increased in recent years (Graph 1). This is not due to a transfer of cases from Type III to Type VIII because of more precise bacteriological work. It will be seen on comparing

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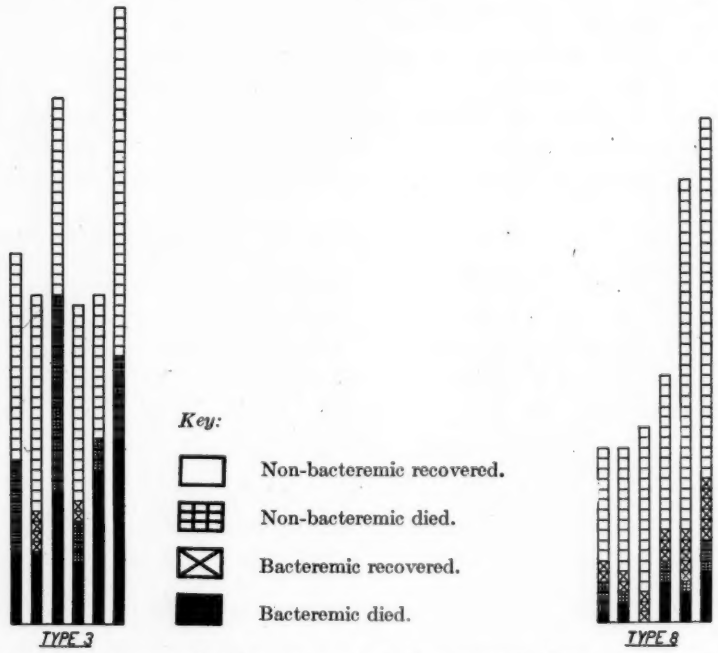
the two types that the number of cases of Type III has increased also.

Pneumococcus Type VIII (Cooper). In June, 1928, Sugg, Gaspari, Fleming and Neill[2] reported on a virulent strain of pneumococcus which is immunologically related to but not identical with typical strains of Type III pneumococci. They definitely avoided the term "sub-type" or "atypical" and referred to it as the "Thomas" strain. They showed that the Thomas strain was precipitated in low dilutions with anti-Thomas serum. In an accompanying paper by Harris, Sugg and Neill,[3] it was shown that rabbits were more susceptible to the Thomas strain and mice more responsive to typical Type III.



GRAPH 1.—Annual admissions for each of 6 years, 1928–1929 to 1933–1934, of patients suffering from pneumonia due to pneumococcus Type III and to pneumococcus Type VIII.

In 1929 Cooper, Edwards and Rosenstein[4] recovered from four strains obtained from Harlem Hospital an organism which was identical with Group IVA found by Robinson[5] to be the most common strain of Type "IV" in 1927 in Pittsburgh, Pa., and with the Thomas strain of Sugg and his coworkers. It was suggested in this article that part of the therapeutic failures with Type III serum might be due to failure to exclude cases due to this type which the authors named Type VIII.

Differentiation. *Morphology.* In a subsequent article by Cooper, Rosenstein, Walter and Peizer,[6] based on a study of 31 strains, the marked cross-agglutination between Type VIII and Type III was again emphasized. The capsule of Type III pneumococcus is usually much larger than that of Type VIII. Type VIII was never found to have the large mucoid colonies characteristic of Type III. There is much more hemolysis about the smaller colonies produced by Pneumococcus Type VIII. Cooper suggested that if agglutination and precipitation reactions are chiefly relied upon for the identity of Type III strains, Type VIII might be confused with it. She suggested that titration of strains should be made with both antisera, which she carried to high dilutions, when organisms reacting with either type are encountered.

Miss Clapp, of the Lederle Laboratories, Inc., informs me that only about 50% of rabbits, in response to the injection of Pneumococcus Type III, produce pure homologous agglutinins for Type III; almost one-half produce some agglutinins for Type VIII as well. When injected with Type VIII strains the rabbits rarely produce agglutinins for Type III. On this account, differentiation of Types III and VIII should be done with rabbit serum tested to contain only agglutinins for one type. Agglutination may not run parallel with "swelling" reaction. Serum which causes good "swelling" reaction should be used for the Neufeld test. All our cases of Types III and VIII for the past 2 years have been checked by Neufeld "swelling" reaction, using specific rabbit serum, a method of differentiating these two types introduced into our laboratory by our bacteriologist, Clare Wilcox. Finland and Winkler[7] found agglutinins for the related type in patients recovering from infections with Type III and Type VIII, a finding we have had an opportunity to confirm. Occasionally both types of pneumococci have been found in the same sputum.

Errors in diagnosis of pneumococcus type can be prevented by checking, with rabbit serum, for the "swelling" reaction, all pneumococci recovered from sputum or cultures of patients or mouse blood. In our earlier work we temporarily mistyped 2 of 15 cases as Type III.

Chain Formation. Pneumococcus Type VIII has the tendency to occur in chains in broth cultures of the blood of mice, and exceptionally in that of patients. Chaining is usually associated with a less severe disease as if the virulence of the organisms were diminished.[13] When found in the blood of patients chain formation should not be relied on either to foretell recovery or as a reason for omitting serum treatment because the agglutinins which produce it may disappear. The occurrence of chain formation and the fate of patients in whom the pneumococcus occurred in chains is shown in Table 1.

TABLE 1.—CHARACTER OF DISEASE IN PNEUMOCOCCUS PNEUMONIA TYPE VIII (COOPER). CASES WITH ORGANISMS IN CHAIN FORMATION, 1928 TO 1933.

Recovered from			
Mouse heart culture.	Lung suction.	Blood culture.	Character of disease.
+	..	..	Moderate
+	..	..	Moderate
+	..	..	Moderate
+	..	..	Moderate
		+ (1 day only)	Moderate
+	..	−	Severe
	+	..	Severe
		+ (1st) − (2d)	Fatal
+	+	+ (Not in P.M. pericardial fluid)	Fatal

Moderate, 5 cases; severe, 2 cases; fatal, 2 cases. + = organisms in chains. − = blood culture sterile.

The Disease as Seen in Man. There are as yet no physical criteria by means of which one can postulate with great probability that a patient who is suffering from pneumonia is infected with Pneumococcus Type VIII.

Invasion. In our cases the onset occurred with a head or chest cold in 23% of the cases, with a chill or chilly sensations in 75% and with pain in the chest in 89%. These symptoms were not especially severe (Table 2).

We have observed that Type VIII pneumonia patients do not, as a rule, appear very acutely ill at first. Clinicians with sufficient experience might well question a report of Type III from a patient who is not severely prostrated and request verification of the type from additional studies and fresh specimens of sputum.

Rating. In our service, cases are rated for severity in accordance with a system already published. The rating is given on admission and is significant in expressing the condition of the patient before therapeutic measures are applied. The characterization of the course, on the contrary, is intended to be an appraisal of severity, made after termination of the disease. Severe cases were fatal, or for some time had a temperature above 103.6° F. or pulse above 120 and other menacing symptoms. They had ratings below 50 at some time. Moderate cases never received rating below 50. Mild cases are those whose rating was never below 70. The relative frequency of severe, mild and moderate cases in Types VIII and III, and the mortality in severe cases, are contrasted in Graph 2. Among the Type III pneumonias there were more severe cases (42%) than there were among the Type VIII pneumonias (26%). More mild cases occurred among the Type VIII cases (47%) than among those due to Type III (15%). The severe cases were more numerous among the Type III pneumonias (42%) than among those caused

by Pneumococcus Type VIII (15%). Many more of the severe Type III cases (78%) died than the severe Type VIII cases (45%). Temperature always below 102° F. was observed in 5% of the Type VIII cases, and pulse below 110 was observed in 11%.

TABLE 2.—OCCURRENCE OF SYMPTOMS AND EFFECT ON OUTCOME AMONG 122 ADULT PNEUMOCOCCUS PNEUMONIAS TYPE VIII (COOPER) OF WHOM 106 RECOVERED AND 16 DIED.

	All cases with symptom.	Per cent of total (122) cases.	Fatal cases with symptom.	Per cent occurrence of symptom in all fatal (16) cases.	Per cent fatality among cases with symptom.
Onset:					
Preceded by cold in head or chest	28	23.0	2	12.5	7.1
Chill at onset	92	75.4	11	68.8	12.0
Pain in chest	109	89.3	15	93.8	13.7
Course:					
Temperature always below 102° F.	7	5.7	0		
Pulse always below 110	14	11.4	1	6.3	
Symptoms:					
Cyanosis	52	42.6	10	62.5	19.2
Anoxemia (requiring O_2)	49	40.2	13	81.3	26.6
Headache	67	54.9	7	43.8	10.4
Apathy	23	18.9	3	18.8	13.0
Irritability	7	5.7	3	18.8	42.9
Sleeplessness	39	32.0	5	31.3	12.8
Delirium	18	14.8	8	50.0	44.4
Sedatives*	83	68.0	12	75.0	14.5
Hiccough	2	1.6	0		
Herpes	3	2.5			
Vomiting	25	20.5	3	18.8	12.0
Diarrhea	1	0.8	1	6.3	100.0
Distention	48	39.3	12	75.0	25.0
Icterus	2	1.6	0		
Pulmonary edema	5	4.1	5	31.3	100.0
Dehydration	5	4.1	3	18.8	60.0
Kahn positive†	28	54.9	3	100.0	10.7

* Sedatives because of pain, sleeplessness or delirium.

† Only 51 cases out of 122 cases were studied for Kahn, of whom 48 recovered and 3 died.

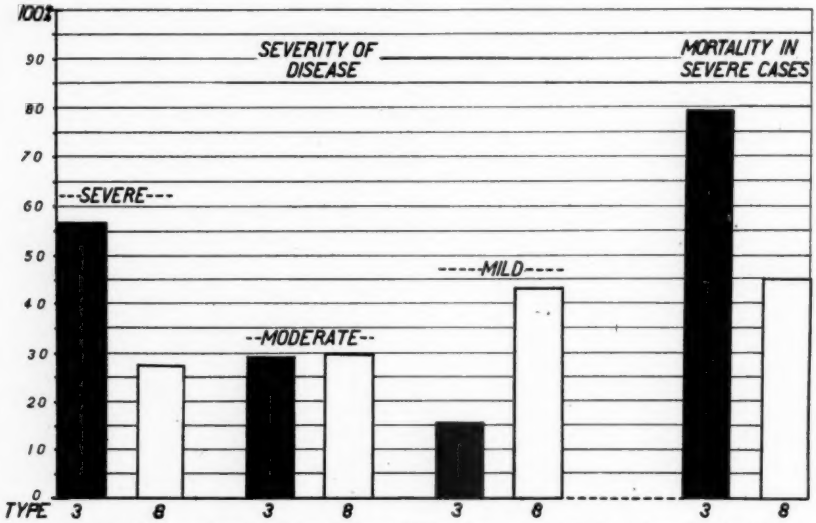
Other symptoms are listed in Table 2. Diarrhea, pulmonary edema and dehydration are seen to be of serious omen. Apparently the occurrence of a positive Kahn reaction was unimportant. It is significant that 40% of the Type VIII bacteremias occurred in mild and moderate cases. The recovery of a patient whose blood was invaded by Pneumococcus Type III was extremely rare.

Termination. Among the 106 cases who recovered, 32 (30.1%) terminated by crisis and 74 (69.8%) ended by lysis.

Physical Signs. The physical signs may be quite classic and well defined, involving an entire lobe. On the other hand there are

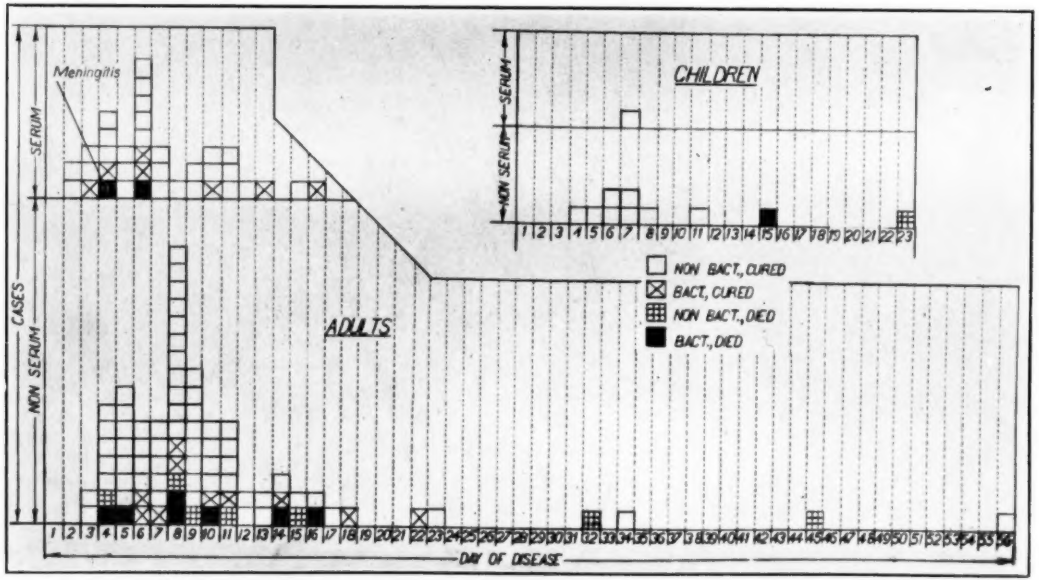
many more cases in which an entire lobe is not consolidated or the consolidation becomes manifest more slowly. There may be only slight dullness, or breathing is distant and the tubular characters not pronounced.

Roentgen Ray. The radiographs of Type VIII pneumonias frequently show involvement of part of a lobe and are less radiopaque than in pneumonias due to types with more dense consolidations, such as Type III. Type III has a tendency, not seen in Type VIII, for the pneumonia to migrate from lobe to lobe.

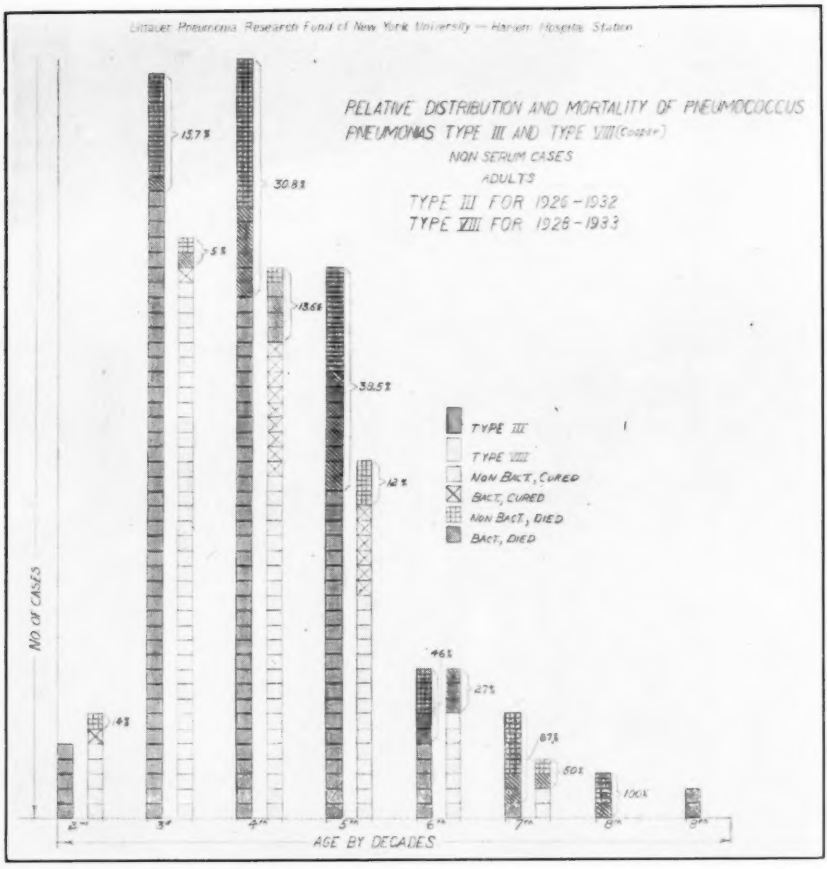


GRAPH 2.—Comparison of Types III and VIII (Cooper). Adults. Type III for 1926–1932. Type VIII (Cooper) for 1928–1933.

Sputum. Bloody or rusty sputum is encountered in pneumonia cases produced by Pneumococcus Type VIII. It is our experience that frank blood in the sputum occurs most frequently in pulmonary tuberculosis, but hemoptyses, indistinguishable from those encountered in tuberculosis, are seen in pneumonia. In the presence of consolidation and hemoptysis we must suspect, in addition to pulmonary tuberculosis, pneumonia due to either B. Friedländer or Pneumococcus Type III or Type VIII. Pneumonia due to B. Friedländer is relatively infrequent 1%, whereas pneumococcus pneumonia due to Type VIII or Type III, in the period from 1928 to 1934, constituted 22.2% of all our pneumococcus pneumonias. The frequency of the occurrence of different kinds of sputum in pneumonia due to Pneumococcus Type VIII and to Pneumococcus Type III may be compared. Rusty or bloody sputum occurred in both types in over 40% of cases but was associated with a fatal outcome in Type VIII cases much less frequently than in the case



GRAPH 3.—Day of termination and outcome. Pneumococcus pneumonias Type VIII (Cooper). 122 adults, 11 children; 1928–1933.



GRAPH 4.—Relative distribution and mortality of pneumonias due to pneumococcus Type III and to pneumococcus Type VIII by decades. The cases in brackets with percentages were fatal.

of Type III. Suppression of sputum was of much graver significance in pneumonias due to Pneumococcus Type III than in pneumonias due to Pneumococcus Type VIII.

Pleurisy. Pleurisy occurred in 26.2% of cases (Table 3). Empyema supervened in 3 instances, 2.4%. The table also gives the relation to transthoracic aspiration of lung juice (lung suction) for diagnosis of type, to pleurisy. This procedure does not seem to have caused pleurisy or empyema, or to be associated with increased mortality.

TABLE 3.—PLEURISY STUDY OF 122 CASES IN ADULTS IN RELATION TO LUNG SUCTION. INCIDENCE OF PLEURISY, 26.2 PER CENT; INCIDENCE OF EMPYEMA, 2.4 PER CENT (3 CASES).

	Cases.	Deaths.
Pleurisy without lung suction	15	1
Pleurisy before lung suction	16	0
Pleurisy after lung suction	1	0
Total	32	

Bacteremia. One of the features of pneumonia which seems to be characteristic of each type is the frequency and severity of bacteremia.[9] Graph 8 shows the relatively low bacteremic incidence of Type III cases (12%) as contrasted with Type VIII (20%). In the non-serum cases the bacteremic mortality for Type VIII is 42%, and for Type III 100%. (The statistics for Type III include cases collected since 1926 and for Type VIII since 1928. Checks of the Sabin typing by Neufeld technique have been done for about 18 months. It is not probable that the percentages are greatly in error, as since 1928 the typings were checked by the appearance of the organisms in smears and in many cases by agglutination to titer in Type VIII antiserum in Miss Cooper's laboratory.)

The importance of bacteremia is shown when we consider the mortality experience from this angle. Among 16 fatal cases 9 had a bacteremia (56.2%) and among 106 who recovered there were only 18 with bacteremia (17%).

The degree of bacteremia, with the outcome, is given in Tables 4 and 5 for serum treated and non-serum treated cases. In the non-serum treated cases the occurrence of few organisms, as indicated by their recovery only in the broth cultures, was less fatal than when they were numerous on the plates. Two cases sterilized their blood though infected to the extent of 30 colonies or more per cc.

Duration of Cases. Graph 3 shows the duration of cases with and without serum. It will be seen that even without serum the most frequent day for termination was the eighth, and that more cases terminated on or before than after that day. With serum the termination was usually sooner than the eighth day. The days of serum administration are given in Table 6.

Agglutination Study. The day agglutination was performed and the result (stained slide agglutination technique) is given for serum

TABLE 4.—BACTEREMIA AMONG 17 NON-SERUM TREATED CASES.
BLOOD INVASION AND OUTCOME.

Sex.	Age.	Year.	Hist. No.	Out-come.	Day of disease.																
					1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.	16.	17.	18.
M.	49	1932	2750	R.	..	Br	..	..	—													
M.	42	1930	4721	R.	..	..	Br	..	..	—												
M.	30	1930	6367	R.	..	1 0	..	—														
M.	42	1930	5874	R.	..	..	..	1 0	..	Br												
M.	32	1931	13615	R.	..	..	..	..	..	..	..	Ch Br	—									
F.	18	1928	4113	R.	..	..	..	..	..	..	Br	Br										
F.	51	1931	12305	D.	..	..	Br	Br	D.													
M.	30	1931	13107	D.	..	..	..	..	..	..	—	PM Br D.										
M.	50	1931	17267	D.	..	..	—	..	..	—	—	—	—	—	—	..	..	PM Br D.				
M.	23	1928	3818	D.	..	..	..	..	1 7	..	..	— D.										
M.	30	1933	30586	D.	..	..	26 28	..	150 152	50 46	2 2	Br	Br	—	—	..	..	..	..	..	..	*
F.	32	1929	4329	R.	..	46 30	11 17	8 4	Br	—												
M.	43	1933	30341	R.	..	..	..	..	12 15	33 30	Br	..	Br	2 0	7 0	7 8	4 0	3 0	Br	..	—	—
M.	36	1928	3850	R.	..	..	..	..	55 65	6 1	—											
M.	60	1933	29399	D.	..	..	..	..	..	..	..	Ch 2 5	..	10 14	Br	..	..	..	—	D.		
M.	54	1932	26997	D.	..	..	116 88	D.														
M.	38	1932	25548	D.	..	—	..	Br	35 50	480 500	640 284	15 5	∞ †	D.								

— = negative culture; PM = postmortem heart blood.
* Death from Type VIII meningitis 3 months later.
∞ † Overgrown.
Br. = broth, Ch. = chained organism, D = died.

TABLE 5.—BACTEREMIA AMONG 10 SERUM-TREATED CASES.
BLOOD INVASION AND OUTCOME.

Sex.	Age.	Year.	Hist. No.	Out-come.	Day of disease.									
					1.	2.	3.	4.	5.	6.	7.	8.	9.	10.
F.	34	1930	3883	R.	Ch Br	— S								
M.	38	1929	4443	R.	..	Br	Br	S						
M.	46	1932	21818	R.	..	..	Br	S						
M.	41	1931	16783	R.	—	—	1 0	—	S					
M.	41	1933	29577	R.	..	..	..	Br	S					
M.	36	1933	30525	R.	..	—	S	—	S	Br	—	..	..	—
M.	39	1933	30912	R.	..	..	..	25 + 51	S					
M.	27	1931	14076	R.	..	..	..	..	..	14 + 20	..	S	..	—
M.	32	1932	4609	D.	..	400 + 500 S	320 + 300 S	D. S	Meningitis					
M.	36	1932	19771	D.	..	..	1600 1760	1790 1080 S	141 *	D.				

Cultures: Blood 1 cc. in broth 50 cc.; blood 1 cc. in each of two agar plates.
S = serum given on these days. * = serum exhausted. Ch = chained organism.

and non-serum cases in Table 7. Among the fatal cases there is only 1 case with agglutination present. The supply of serum was exhausted and immunity was then lost in that case.

TABLE 6.—DATA OF 37 SERUM TREATED CASES OF TYPE PNEUMONIA.

Hosp. No.	Age.	Rating.	Day of illness treated.	Units given.	Reaction.	Day disease terminated.	Outcome.
30912	39	70	5–6	46,500	Twitching, spots before eyes	6th	Recovered
29452	28	80	4–5–6	66,000	None	9th	"
6742	29	55	8–9	87,200	None	11th	"
7323	25	65	9	24,000	Flushed (1st dose only)	10th	"
7623	38	80	9–10	60,000	None	12th	"
13892	25	40	3–4–5–6–7–10–11	193,000	None	11th	"
19712	51	60	....	96,000	Cyanosis; severe chill; elevation of temp. to 107°	11th	"
21585	50	80	5	20,000	Temp., 105°; chill	8th	"
29577	41	57	5–6	35,000	None	10th	"
30525	36	55	3–4–5	38,500	None	13th	"
14076	27	58	8–9–10–11–12–13	277,800	None	16th	"
4609	32	65	2–3	92,800	None	4th	Died
19771	36	60	4–5–6	136,000	Headache	6th	Died
4443	38	62	3	16,000	Nausea; severe chill	3d	Recovered
4522	39	55	2	10,400	Sweating; coughing; faintness; chill	2d	"
4660	32	80	1	8,000	None	5th	"
4745	33	78	3–4–5	24,000	None	3d	"
4807	15	80	7–8–9	172,000	None	10th	"
3883	34	50	2–3	52,000	None	3d	"
4723	47	85	2	29,600	None	2d	"
5315	28	70	5–6	58,200	Urticarial eruption, itching, pain in joints of hands, serum sickness	6th	"
6642	41	35	2–3–4–5–6–7	235,360	None	6th	"
12956	28	75	5–6	78,000	None	6th	"
15460	22	90	4	8,000	Severe chill 2 hours later	4th	"
15880	38	70	3–5–6	105,000	Chill after last dose	7th	"
16783	41	50	4–5	24,000	None	6th	"
21818	46	85	3–4	54,800	None	4th	"
22386	43	85	4	4,000	Severe chill	4th	"
24042	36	..	8–9	36,000	None	9th	"
26288	27	60	6–7–8–9	164,000	None	15th	"
26132	25	75	4–5–6–7	40,400	Vomiting, chilly sensation, profuse sweating	7th	"
27179	13	90	5	12,000	None	6th	"
28845	23	85	2–3–4	25,000	Severe chill, perspiration	4th	"
28842	40	85	3–4	20,000	None	5th	"
16387	26	75	5–6	23,000	Skin rash	6th	"
29648	32	65	6–7	18,000	Slight chill	7th	"
30863	13	70	5	12,500	Chill	5th	"

All serum was administered intravenously.

Complications and Associated Diseases (*Table 7*). There were 3 cases of empyema due to Pneumococcus Type VIII; 2 recovered. One of these cases returned 3 months after discharge (after this

TABLE 7.—AGGLUTINATION STUDY OF PNEUMOCOCCUS PNEUMONIA TYPE VIII (COOPER) IN ADULTS.

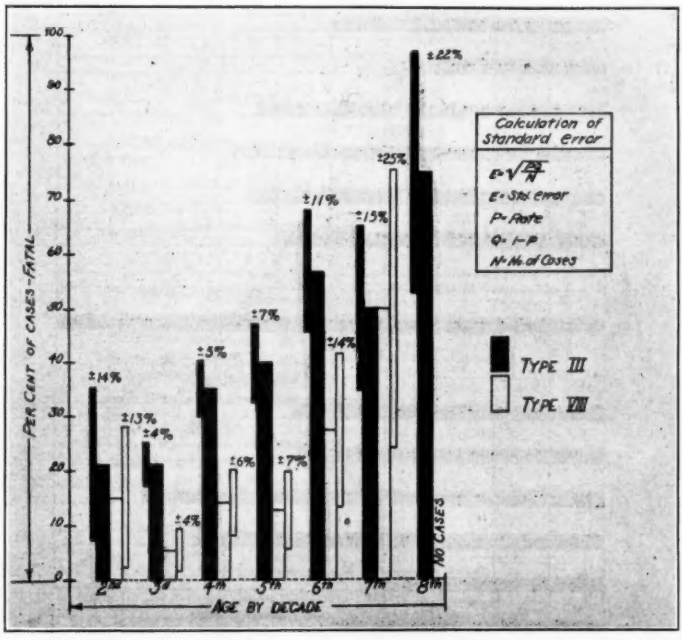
	Serum.					Non-serum.				
	Recov. cases agt. +	Recov. cases agt. −	Fatal cases agt. +	Fatal cases agt. −	Total cases studied.	Recov. cases agt. +	Recov. cases agt. −	Fatal cases agt. +	Fatal cases agt. −	Total cases studied.
Cases studied	19	8	1	1	29	11	22	0	3	36
Day of illness:										
1st										
2d	..	3								
3d	3	3	1	..	..	..	1			
4th	3	6	..	1	..	4	3			
5th	8	4	..	1	..	1	2			
6th	6	..	..	1	..	1	10	..	2	
7th	7	5	..	..	..	..	13	..	1	
8th	6	3	..	..	..	1	8	..	1	
9th	4	5	..	..	..	2	11	..	2	
10th	6	3	..	..	..	..	8	..	3	
11th	4	1	..	..	..	2	5			
12th	1	2	..	..	..	1	7			
13th	2	4	..	..	..	1	7			
14th	1	1	..	..	..	2	2			
15th	..	4	..	..	..	1	1			
16th	1	4	..	..	..	1	1			
17th	..	2	..	..	..	1	1			
18th	..	2	..	..	..	1	2			
19th	..	2								
20th	1	1	..	..	..	..	1	..	1	
21st	1									
22d	..	1	..	..	..	..	3	..	1	
23d	1	..	..	..	..	..	1			
24th	1	..	..	..	..	..	2			
25th	..	..	..	..	..	..	2			
26th	..	1	..	..	..	1	1			
27th	..	1	..	..	..	1				
28th	..	1								
29th										
30th	..	..	..	..	..	..	1			
31st										
32d	1	..	..	..	..	..	1			
33d										
34th	1	..	..	..	..	..	1			
35th										
36th										
37th										
38th										
39th	1	1								
Determinations (days)	59	60	1	3	123	21	95	0	11	127

series was collected) and died of a meningitis due to Pneumococcus Type VIII. A fatal empyema case occurred in a patient with tuberculosis. It is our impression that Pneumococcus Type VIII is

more frequently encountered in the sputum of patients with pulmonary tuberculosis than pneumococci of other types.

Albuminuria. Only 4 patients showed marked albuminuria; they all recovered and the albuminuria disappeared.

Age and Sex Distribution and Mortality. Graph 4 presents the frequency of occurrence of pneumonias due to Types III and VIII, and the outcome in bacteremic and non-bacteremic cases divided into decades. It is readily seen that most of the cases of both types occurred before the fortieth year. In this graph the mortality of bacteremic and non-bacteremic cases is indicated. In Graph 5 the



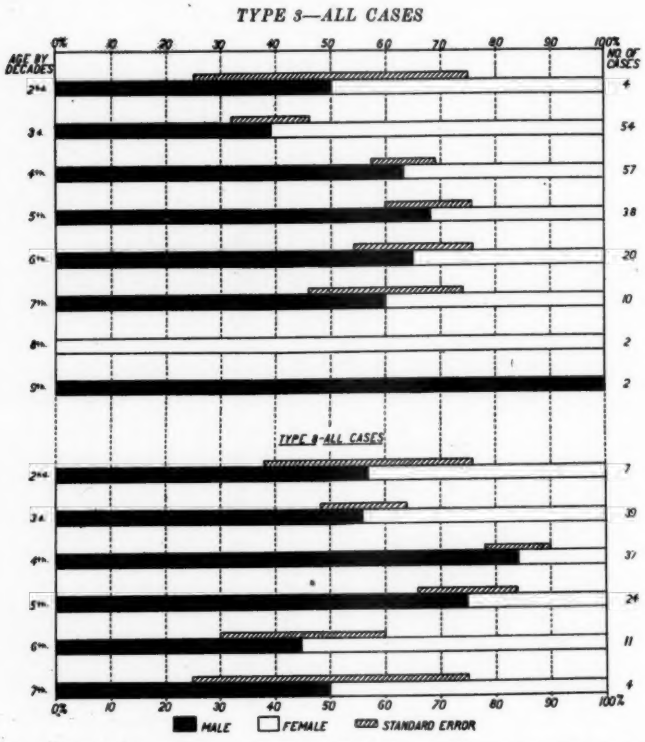
GRAPH 5.—Relative mortality rate of pneumococcus pneumonias Type III and Type VIII, according to age. Type III for 1926–1932. Type VIII for 1928–1933.

mortality is considered separately by decades for these two types. The standard error of observation is indicated by the bayonet. There is a much greater mortality in Type III than in Type VIII except in the seventh decade, where they are equal. Type III steadily increases in fatality with a slight fall in the seventh decade. Type VIII continued relatively low through five decades and then increased rapidly in the sixth and seventh.

The sex distribution is given in Graph 6. It will be seen that there is no marked selection of older females in either type and certainly the older females are not selected by Pneumococcus Type III as opposed to Pneumococcus Type VIII, as found by Blake[10]

and by Finland and Sutliff.[11] Males predominate in both types at almost all ages. This is true of many types.

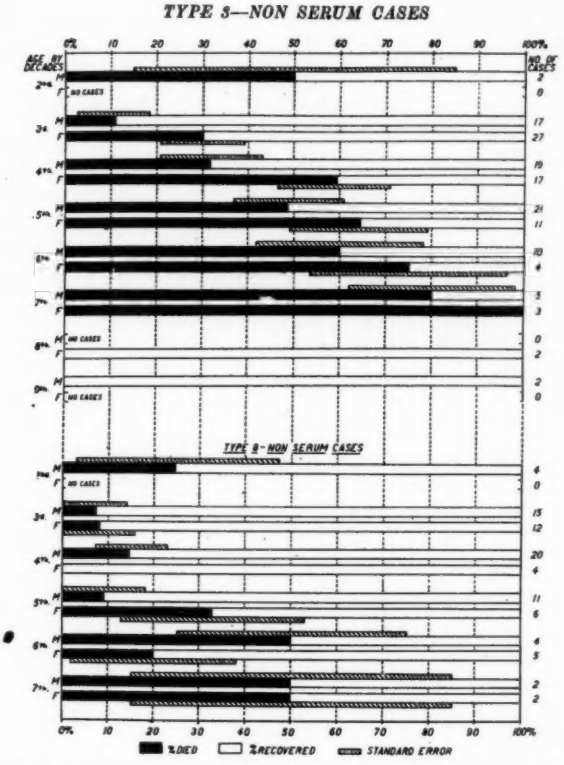
The mortality in the two types by sex is given in Graph 7. In this graph only the non-serum cases were considered so as to have an uninfluenced death rate for comparison. In all decades the female mortality for Type III is higher than the male. Only in the third decade are the cases sufficiently numerous and the difference in percentage significant.



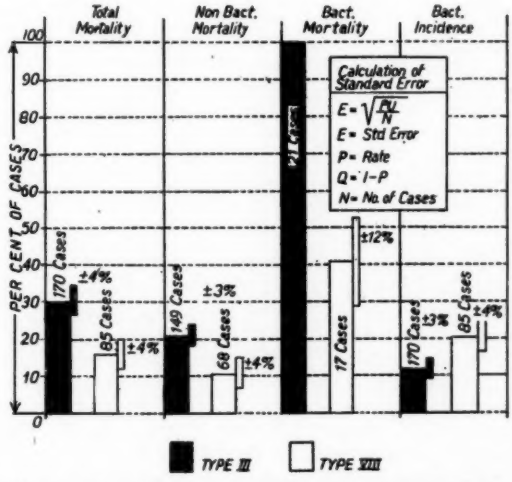
GRAPH 6.—Relative occurrence in sexes by Age. Pneumococcus pneumonias. Type III for 1926–1932; Type VIII (Cooper) for 1928–1933, all cases.

Our experience does not coincide with that of Blake or of Finland and Sutliff that older females are the chief victims of Type III. In the Type VIII cases the preponderance of female deaths does not occur. Though there are more deaths among women the error in the sampling is too large for the difference to be significant at this time.

Graph 8 shows, for the non-serum cases from 1928 to 1933, that the bacteremic mortality is less in Type VIII (40%) than in Type III (100%), and the non-bacteremic mortality is also less, 10% in Type VIII and 21% in Type III. The results are reflected



GRAPH 7.—Male and female mortality by age. Pneumococcus pneumonias. Type III for 1926–1932; Type VIII (Cooper) for 1928–1933, non-serum cases.



GRAPH 8.—Incidence of bacteremia and fatality. Pneumococcus pneumonias, Type III and Type VIII (Cooper). Non-serum cases, 1928–1933.

in the total mortality (bacteremic and non-bacteremic) which are almost twice as great in Type III as in Type VIII—30 and 16% respectively.

It is significant and fortunate that though bacteremic incidence of Pneumococcus Type VIII is much larger than in Pneumococcus Type III, the mortality is much lower in bacteremic Type VIII cases.

Therapeutic Serum. The development and use of serum for Pneumococcus Type VIII pneumonia has been reported elsewhere.[12] The details of the treatment, including day of illness on which treatment was given, the rating, method, day of termination and outcome, are given in Table 7. The effect of serum treatment on mortality is given in the table. The effect in shortening the disease is shown both in Graph 3 and in Table 7. In severe cases the saving of lives was striking. There were 12 cases with 2 deaths (16%) in the serum group, and 21 cases with 14 deaths (61.9%) in the non-serum group. There were 6 bacteremic cases with 2 deaths (33.3%) which received serum, and 10 cases with 7 deaths (70%) among the non-serum cases.

Children. Pneumococcus Type VIII is not a frequent invader of children and description of the type of pneumonia it causes must await further observations.

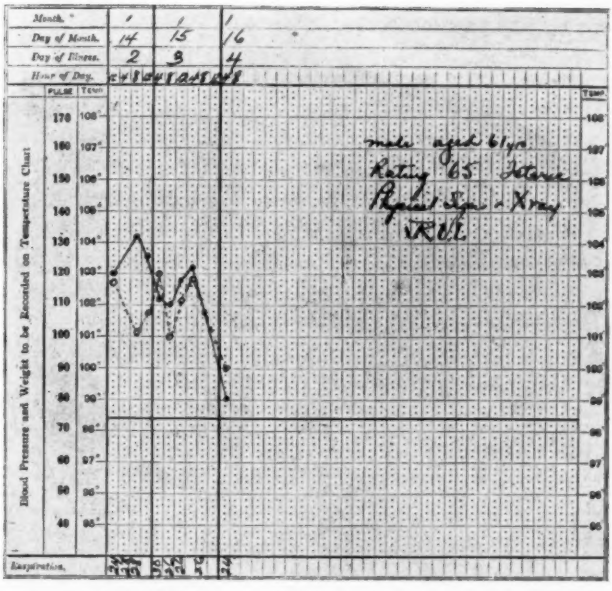
We have selected several case histories which exemplify the character of the disease.

Case Abstracts. *A Moderate Case.* H. C., a man, aged 61, was admitted to the hospital on the second day. He was rated at 65. He was icteric, with physical signs and Roentgen ray confirmation of the consolidation of the right upper lobe. His temperature and pulse were normal on the morning of the 4th day. There was considerable albumin in his urine. Case 1.

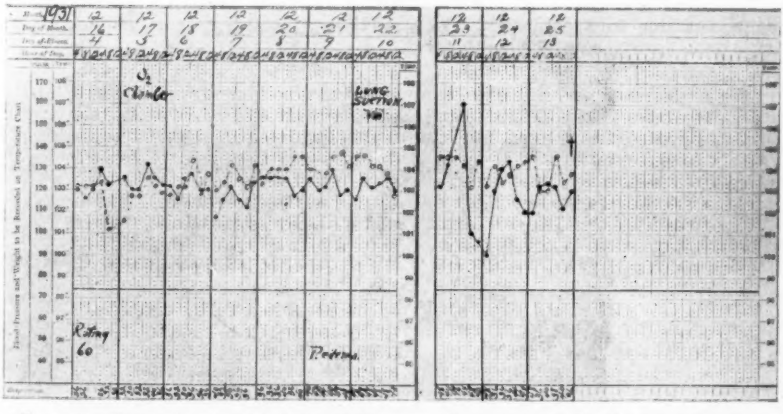
A Fatal Case. B. W., a man, aged 50, was admitted on the 4th day of his disease with a temperature of 103° F. and a pulse of 122. His respirations were 36. He was admitted to the oxygen chamber because of cyanosis and dyspnea on the 5th day. His blood count was 3100; neutrophils, 2480 and lymphocytes, 620. He continued severely ill and developed pulmonary edema on the 9th day of the disease. On the 10th day a lung suction gave Pneumococcus Type VIII. On the 13th day he died with pulmonary edema. His blood count was 6900; neutrophils, 5200 and lymphocytes, 1600. Case 2.

Spontaneous Pneumothorax Associated With Tuberculosis and Pneumococcus Type VIII Pneumonia. Another patient is S. W., who was admitted with a temperature of 105° F., pulse, 128 and respirations, 46. He had the signs of a pneumonia and a left pneumothorax. His white blood cell count was 25,000; neutrophils, 23,250 and lymphocytes, 1750. On the 3d day we recovered Pneumococcus Type VIII from the mouse heart inoculated with his sputum on the 5th day. On the 4th day the chest fluid was sterile. Tubercle bacilli were recovered in the sputum. Roentgen ray revealed a large pneumothorax with five cavities in the upper portion of the left lung, with fluid at the base and a fibrotic tuberculosis involving the right apex. On the 14th day there was pus in the left chest, which con-

tained Pneumococcus Type VIII. On the 27th day his condition was so poor that he required a transfusion; 16 days later he died. A thoracotomy had been performed. Case 3.



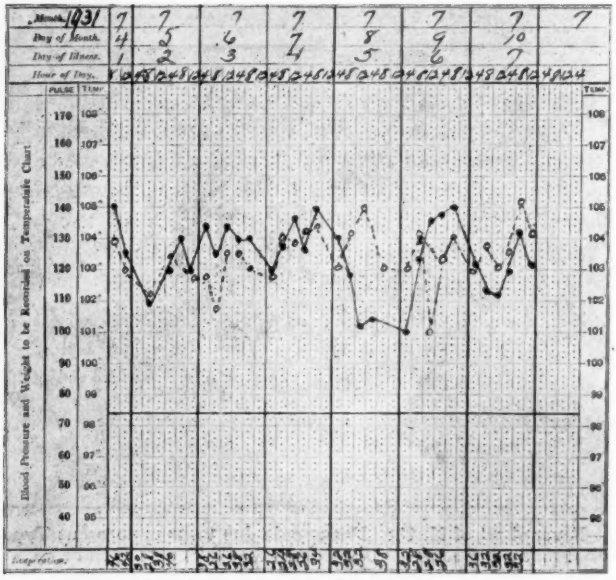
CASE 1.—Fever chart of H. C.: Pneumonia due to pneumococcus Type VIII. Moderately severe. Temperature normal on fourth day.



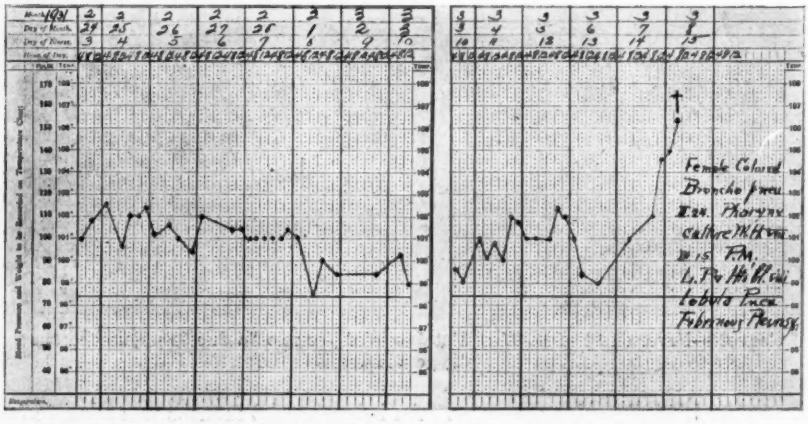
CASE 2.—Fever chart of B. W.: Fatal case of pneumonia due to pneumococcus Type VIII.

Infant With Bronchopneumonia. An infant aged 9 months was admitted with bronchopneumonia on the 3d day. Temperature fluctuated between 102.6° F. and normal until the 14th day. On that day the temperature rose to 106.2° F. and the baby died. On the 13th day the temperature had been normal. On the day of admission a pharyngeal culture was

made. The mouse inoculated revealed a Type VIII in its heart's blood. The postmortem lung suction and heart's blood of the patient contained numerous pneumococci Type VIII. The autopsy revealed a lobular pneumonia and a unilateral fibrinous pleurisy. This case exemplifies the occurrence of partial immunity which is later lost. This seems to be frequent in invasions by this pneumococcus. Case 4.



CASE 3.—Fever chart of S. W.: Pneumococcus pneumonia in patient with pneumonia due to pneumococcus Vype TIII complicated by pyopneumothorax. Onset with spontaneous pneumothorax.



CASE 4.—Fever chart of infant with bronchopneumonia due to pneumococcus Type VIII.

Late Complication. A non-serum case cleared his blood stream, had an empyema, operation and was discharged as cured. Three months later he returned with a pneumococcus Type VIII meningitis, and died. Case 5.

TABLE 8.—COMPLICATIONS AND ASSOCIATED DISEASES AMONG 122 ADULT CASES.

Complication or associated disease.	No. of cases.	Bacteriology and remarks.	Outcome.	
			Recovered.	Died.
Empyema	4	1 hem. strep. after Type II (secondary infection)	1	
(No lung suction on these cases)		3 pneumococcus Type VIII*	2	1
Meningitis	1	Pneumococcus Type VIII	..	1
Otitis media	1	Not due to pneumococcus Type VIII	1	
Nephritis	4	Marked albuminuria	4	
Epilepsy	1	.....	1	
Emphysema	1	.....	1	
Paget's disease	1	.....	1	
Miscarriage	1	.....	1	
Alcoholism	1	.....	1	
Delirium tremens (alcoholic)	1	.....	1	
Obesity	1	.....	1	
Small fibrotic tuberculous lesion in right intraclavicular region	1	Tubercle bacilli not found in sputum	1	

* The 2 cases who recovered were operated; the fatal case was operated, had a spontaneous pneumothorax with a tuberculosis, and had positive sputum.

Summary. Based on 122 cases in adults and 11 cases in children, a rough sketch of the disease produced by Pneumococcus Type VIII is given. It is usually of less severity than the disease produced by some of the other pneumococci. It is much less serious than pneumonia due to Pneumococcus Type III. The organism invades the blood more frequently than does Pneumococcus Type III, but with a much smaller mortality. It produces bloody sputum frequently. Occasionally it may be associated with pulmonary tuberculosis. It is treacherous, invading the meninges or the blood stream after apparent subsidence of symptoms. This may be due to the development of a focus which subsequently ruptures and releases virulent organisms. When organisms recovered from the sputum occur in chains the cases are, on the average, less severe. When in cultures of subsequent sputa or blood the chaining disappears, the organisms are virulent or resistance has been lost. The organisms do not invade the older age groups with especial frequency. The age distribution is similar, in our experience, to that of Type III, except that the latter is more frequent in children. Agglutinins are formed and can be readily transferred in therapeutic serum. When demonstrable agglutinins do not develop the patients are less apt to recover.

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GIARDIA INFESTATION OF GALL BLADDER AND INTESTINAL TRACT.

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THE flagellated protozoön *Giardia intestinalis* was first observed and vividly described by Leeuwenhoek.[1] In the course of subsequent studies it has been variously named *Cercomonas intestinalis* (Lambl[2]), *Dimorphus muris* (Grassi[3,4]) *Megastoma entericum* (Grassi[4,5]), *Giardia* (Künstler[6]), *Lamblia* (Blanchard[7]), and *Lamblia duodenalis* (Stiles[8]). Kofoid and Christiansen[9] consider the terminology *Giardia lamblia* correct, but Lambl's original specific name *intestinalis* persists, and the organism is most frequently referred to as Lamblia or *Giardia intestinalis*.

The pathogenic rôle of this parasite is still in dispute. Experimental data are meager, and autopsy reports almost non-existent. The following case, therefore seems worthy of report, particularly since the infestation was associated with chronic inflammation of the gastro-intestinal tract and since, at autopsy, the gall bladder was found to be teeming with the invading organisms.

Case Report. J. S., No. 9391, a 57-year-old blacksmith and farmer, was admitted November 15, 1931, for the relief of diarrhea. No other member of his large family was similarly affected. With minor exceptions, his past health had been good. He had never had skin lesions of any kind, nor had his tongue been sore. His teeth had been in poor condition for many years. He had long had a tendency to constipation. There had been no clay-colored or tarry stools. Nycturia (2 or 3 times a night) had been present for many years.

His digestive complaints had begun 16 years previously, with intense burning and sense of fullness in the epigastrium with occasional nausea and vomiting from 10 to 30 minutes after eating. The vomitus is said to have contained undigested food and dark brown blood. At first these symptoms were all relieved by alkalin drugs, but more recently such medication was not effective. Heavy foods such as meats and vegetables made his symptoms worse, and he consequently had limited his diet to soups, eggs, and milk.

Five years before admission his symptoms became so severe that he had to give up his work as a blacksmith, and since that time he had done no hard labor. During the 2 years before admission there was a rapid increase in severity of the symptoms, with loss of weight and weakness so marked as to cause occasional fainting spells. For 14 months preceding hospitalization he had been able to retain only the smallest amounts of liquid food and eggs.

Five days before admission a profuse diarrhea set in, with 10 or 15 dark, liquid stools a day, and he became so weak that hospitalization was imperative.

Physical Examination on Admission. Temperature 37° C., pulse 98, respirations 16, blood pressure 130/95. He was in no acute distress, but appeared tired and chronically ill. The skin was rather dry; the mucous membranes were of good color. There was no generalized lymph node enlargement. Hearing was somewhat impaired, bilaterally. *Eyes:* There was marked impairment of vision, slight anisocoria, and almost no pupillary response to light. Ophthalmoscopic examination showed marked thinning and increased light streak of the retinal arterioles, normal cupping of the disks, and no retinal exudates or hemorrhages. *Mouth:* Teeth were in very bad condition, with several extractions, considerable caries, and marked pyorrhea. The tongue was slightly reddened around the edges only. *Neck* showed no abnormalities. Except for a few râles over the larger bronchi in the right interscapular region the lungs were normal. The *heart* was not enlarged to percussion; the heart sounds at all areas were very distant and were of poor muscular quality at the apex; the second aortic sound was somewhat increased. The abdomen was diffusely rigid; no masses could be felt; lower abdominal scars were present, the result of previous herniorraphy. The *genitalia* were normal. *Rectal* examination seemed to cause considerable pain although there were only a few hemorrhoidal tags to account for it; the prostate was slightly enlarged but contained no masses and was not indurated; there were no abnormal masses in the rectum. The *reflexes* and *neurologic examination* were normal.

Accessory Examinations. Red blood count 4,250,000; hemoglobin 14 gm.% (Sahli); white blood count 19,550; neutrophils 75%; small lym-

phocytes 12%; large lymphocytes 9%; monocytes 4%. The urine was entirely normal. The blood Wassermann reaction was negative. Blood chemistry examinations showed a carbon dioxid combining power of 53.2 volumes%; non-protein nitrogen 47 mg.%; sodium chlorid 386 mg.%.

Repeated bacteriologic study of blood and stools showed no abnormal findings.

Roentgen-ray examination of the gastro-intestinal tract revealed nothing unusual in the stomach or duodenum. The colon had practically emptied 24 hours after the barium meal. Barium enema revealed very marked spasm of the lower descending and sigmoid colon, but the barium passed readily into the other parts of the colon. The cecum was rather small and easily movable. There was loss of the haustral bands distal to the splenic flexure. The roentgenologist was of the opinion that the evidence favored some form of colitis that had been present long enough to produce thickening of the colon wall and that was causing considerable spasm at the time of examination.

Analysis of the *gastric contents* showed many red blood cells and a positive guaiac reaction but no undigested food, Boas-Oppler bacilli, or other evidence of gastric retention. There was no free hydrochloric acid in the stomach contents even after histamin stimulation.

The *vomitus*, examined thrice, consisted of clear liquid and food particles, without gross, microscopic, or chemical evidence of blood. On one occasion it was swarming with actively motile *Giardiæ*.

The *stools*, which were examined frequently, were liquid, brown, and bloody, with a moderate amount of mucus. Microscopic examination showed many red blood cells, and the guaiac and benzidin tests were strongly positive. On the third day after admission, many motile *Giardiæ* were observed; afterward, only encysted forms were found in the stools.

Course in the Hospital. For the first 6 days, the temperature remained normal, although there was an occasional tachycardia. During this time, the patient had from 5 to 7 stools a day. His appetite was poor, and he vomited several times daily. On the 7th day, he became much worse. His diarrhea increased, his temperature rose to 38.6° C., and he appeared much weaker. He refused food and fluid; glucose and saline had to be administered parenterally. All attempts to check the diarrhea, including large doses of opiates and calcium, were futile. In view of the presence of *Giardiæ* in the intestinal contents, one dose of neoarsphenamin (0.45 gm.) was administered, without apparent effect.

From this time on, his course was rapidly downward. His diarrhea increased to as many as 20 stools a day, his appetite failed entirely and he became so weak as to be almost helpless. In spite of all treatment he died on the 12th day after admission.

Autopsy (7½ hours after death). The salient features were as follows: The body was that of a well-developed and moderately well-nourished white male. The visceral and parietal *pleuræ* of both lungs were bound together by old fibrous adhesions, which were more diffuse over the left lung. Both *lungs* contained a small amount of fluid and areas of thickening of the interstitial tissue. The *liver* weighed 1825 gm. Its external surface was smooth. It contained a tumor, 1.5 cm. in diameter, which was made up of many small bloodvessels. The liver also contained a large amount of fat, which, however, was not distributed in any characteristic pattern. There was an increase in the number of mononuclear cells about many of the portal canals.

The *gall bladder* was normal in size, and contained a brownish-black, mucoid secretion. Some of this secretion, before the gall bladder was opened was found to be teeming with *Giardiæ*, most of which were in the vegetative stage. The wall of the gall bladder was partially autolyzed,

FIG. 1.—Superficial ulcers and atrophy of the mucosa in the sigmoid colon in a case of Giardia infestation of the intestinal tract.

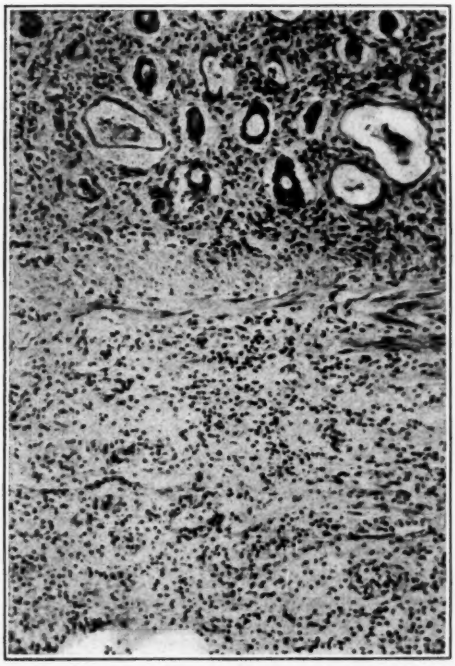

FIG. 2.—Photomicrograph of a part of the colon near one of the ulcers shown in Fig. 1. The inflammatory reaction is pronounced in the submucosa.

and a few mononuclear cells could be seen in portions of the wall. However, no *Giardiæ* could be demonstrated in section. The bile ducts were patent and normal.

The *spleen* weighed 225 gm. and was relatively soft, resembling a mild acute splenic tumor.

The lesions of greatest interest were found in the *intestinal tract.* The lumen of the distal half of the transverse colon and of the descending and sigmoid colon was dilated. The entire tract showed evidence of a chronic inflammatory process in the mucosa and part of the submucosa, these changes being most pronounced in the colon. The mucosa of the colon was atrophied in some areas, while in other areas there were superficial ulcers, some in small clusters, others distributed in a line along one of the tæniæ coli. The margins of these ulcers were ragged and hemorrhagic and the bases slightly necrotic. The largest ulcer, which was located 8 cm. from the anal margin, measured 6 or 8 mm. in diameter and extended down into the muscularis. In addition to the ulcerated areas in the colon, portions of the mucosa were covered by a diphtheritic membrane. In the ulcerated areas there were many Gram-positive and Gram-negative bacteria, the predominating organism being a Gram-positive, elongated diplococcus. No *Giardiæ* were found.

Discussion. *Pathogenicity.* The question of whether or not *Giardia* is pathogenic for man is still undecided, opinion being about equally divided. Wenyon,[10] Fantham and Porter,[11] Lyon and Swalm,[12] Smithies,[13] and Heubner[14] are of the opinion that it may cause clinical symptoms; but Boeck[15] takes the position that the arguments so far presented are not conclusive.

Experimental observations are few, but in the main, as for example in the work of Deschiens[16] and of Fantham and Porter,[11] the evidence seems in favor of their being truly pathogenic, although Boeck[15] points out pertinent objections to certain of the experiments.

Autopsy reports likewise fail to solve the problem, because infestation with this organism is apparently rarely fatal. We have been able to find only one autopsy report on this subject, that of Fairise and Jannin.[17] The clinical history was that of chronically recurring diarrhea. Necropsy showed numerous discrete and confluent, fungating ulcers in the cecum, ascending colon, and, to a less extent, the descending colon. These authors also made the significant observation that *Giardia* is not only a surface parasite but may penetrate even to the subserosal coat. They conclude that the organism is pathogenic.

The evidence in our case is by no means conclusive, for *Giardiæ* could not be demonstrated in the intestinal wall even at the site of the ulcers. It is possible, moreover, that the patient's grossly deficient diet was the primary cause of his symptoms, and that the parasite was merely a secondary invader in an intestinal tract already injured as a result of chronic avitaminosis.

Relation to Gall Bladder Disease. Whether or not *Giardia* may give rise to chronic inflammation of the gall bladder is likewise a disputed point. Suspicion has been cast in its direction especially since the introduction of the Meltzer-Lyon method of duodenal

drainage. The literature contains reports of numerous cases in which duodenal aspirates, negative under fasting conditions, yielded large numbers of *Giardiæ* after magnesium sulphate stimulation. This evidence, however, is open to the possible objection, suggested by Boeck, that the flagellates may have been driven out of the glandular crypts by the irritant action of magnesium sulphate.

More trustworthy evidence of their invasion of the gall bladder has been adduced by finding the parasites at operation (1 case by Westphal and Georgi[18] and 2 cases by Smithies.[19]). So far as we have been able to find, ours is the only case in which *Giardiæ* have been demonstrated postmortem in the gall bladder.

It cannot be claimed, of course, that the mere presence of *Giardiæ* in the gall bladder is proof of their pathogenicity. But the fact that they have been found in this organ at operation and now at autopsy makes it fairly reasonable to assume that their demonstration in duodenal aspirates is indicative of their presence in the gall bladder; and it may well be that their invasion could give rise to symptoms of gall bladder inflammation. Further clinical, operative, and autopsy observations will of course be required before their true significance can be determined with accuracy.

Summary. A case is reported of a 57-year-old blacksmith who for 16 years had suffered from intestinal discomfort, consisting at first of epigastric fullness and burning, and progressing to vomiting, loss of weight and strength, and finally severe diarrhea. All studies were normal, except that the stools were teeming with motile *Giardiæ*. These organisms were observed also in the vomitus.

Autopsy revealed a diffuse enterocolitis with atrophy and hyperemia of the mucosa of the duodenum and large intestine, and, in addition, numerous superficial ulcers in the colon. *Giardiæ* were present in the gall bladder bile removed at autopsy.

The possible pathogenicity of this organism and its relation to gall bladder disease are discussed.

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LONG-CONTINUED VACCINE THERAPY AS A CAUSE OF AMYLOIDOSIS.

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Amyloid disease has long been known to be associated with chronic infection, malignancy and more recently with multiple myeloma.[1] Since the latter diseases are frequently accompanied by disturbances in the blood protein levels, especially by an increase in the normal or abnormal globulins it would appear that this common factor is involved in the formation and deposition of an abnormal protein called amyloid substance. Although other factors, such as disturbance of the reticulo-endothelial tissue, may also play a rôle, the experiments of Kuczynski,[2] in which amyloid disease was produced in mice simply by feeding large amounts of casein, seem to show that excess of protein alone may give rise to the disease in certain cases. Other clinical and experimental studies have shown that the blood proteins may be increased by a high protein diet. Our own experiments to be published elsewhere support the idea that amyloid disease frequently follows long periods of hyperglobulinemia. Four rabbits were given approximately 96 intramuscular injections of sodium caseinate over a period of 8 to

13 months. During this time the amount of blood globulins was increased from 2 to 4 times over the normal level. Each of the animals died from extensive amyloid disease.

In 1899 Paltauf[3] noted amyloidosis in horses inoculated repeatedly with antigens for the production of serums. Similar observations have been made subsequently, the most recent by Sipos[4] who found amyloidosis in 80% of the horses used for the production of various serums and vaccines, and by Doerken and Arndt[4] who found the condition in 60% of horses used for similar purposes. Amyloid disease has been deliberately produced in various animals by the repeated injection of a variety of bacterial vaccines, toxins, casein, egg albumin, gelatin, nuclein, zein, peptone, organ transplants, silicates, manganese chlorid, sulphur, selenium, turpentine and other substances.[5] The literature covering these experiments up to 1918 is summarized in the papers of Bailey and Hirose.[6]

Langstein and Mayer[7] in 1904 showed that vaccines when injected into animals led to an increase of blood proteins, especially of the globulins. Similar observations were made subsequently both in animals and in man after the injection of a variety of substances.[8] There is evidence to suggest that the blood proteins are normally formed by various widespread tissue cells.[9] Under the abnormal stimulus of the disturbance which follows parenteral injection of a variety of substances, by infections or neoplasms, the rate of formation is hastened, thereby increasing the amounts of blood proteins over the normal. It is believed that amyloid substance may be the result of the deposition or precipitation in the tissue of the excess amounts of normal globulins[10] or of new abnormal proteins[1] produced under these circumstances.

These facts supported by the discovery of amyloid substance in vaccinated animals, the increase of blood globulins in patients with amyloid disease[11] and by our own unpublished experiments showing a constant hyperglobulinemia in rabbits which ultimately died from amyloidosis, suggest a causal relationship between conditions causing chronic hyperglobulinemia and eventual amyloid disease. With these possibilities in mind there is reason to believe that repeated injections of vaccines or a variety of other substances commonly used for therapy in man may in some individuals be the underlying cause or contributing factor in the formation and deposition of amyloid substance. The following case report illustrates this possibility.

Case Report. Mr. L. L., aged 28, had typhoid fever at the age of 7, pneumonia at 9, chickenpox at 11, smallpox at 14 and dysentery at 19.

In 1925 he noted soreness in the right arm after exercise and gradual stiffness of the shoulder. By 1927 the shoulder was completely ankylosed. In 1929 his left knee became red, swollen and tender 2 days after slight trauma. Following this there was gradual limitation of movement of his left shoulder. By February, 1931, the arthritis had progressed so that crutches were necessary. In March, 1931 an autogenous vaccine was made

from organisms said to have been recovered from the fluid aspirated from the knee. He was given 9 intramuscular injections during the following 3 months. In August he was given an intravenous injection of streptococcus vaccine and was admitted to the Medical Service as a bed patient in September. Between September and March, 1932, 20 intravenous injections of streptococcus vaccine were given at weekly intervals. There was continual fever ranging from 37.2° C (99° F) to 37.8° C (100° F.) during the period of vaccine therapy. His condition improved slightly. On subsequent visits to the Out-patient Department he received 2 more vaccine injections. During July and August, 4 injections were given by his own physician, and in October he received 3 more from another physician.

In November, 1932, blood and mucus appeared in his stool. In December, he vomited much of his food and was jaundiced for 2 weeks. In January there was repeated transient swelling of the eyelids and ankles. His physician then administered 3 more injections of streptococcus vaccine intramuscularly. He improved somewhat but in September, 1933, he vomited most of his food and drink. His temperature was said to have been subnormal 35.6° C. (96° F.). Bloody diarrhea appeared and blood oozed from his nose. In October, 1933, he was readmitted to the hospital with the usual signs and symptoms of uremia. His blood pressure was 107/60, blood urea nitrogen 147 mg. per 100 cc. There was heavy albuminuria and marked anemia. Amyloid disease was suspected although the liver and spleen were not palpable. This impression was confirmed when all of the 200 mg. of Congo red dissolved in distilled water and injected intravenously was absorbed by the tissues in 60 minutes. The blood proteins totalled 4.71 gm. per cent composed of 1.29 gm. fibrinogen, 2.67 gm. globulin, and 0.74 gm. albumin. The patient became comatose, developed pericardial friction and edema of the lungs and died in November, 1933.

Necropsy (Dr. R. W. Koucky): The chief relevant findings were marked amyloidosis of the spleen, liver, kidney and adrenals and the lesions of chronic arthritis. The spleen and adrenals were bright pink due to staining of the amyloid substance by the Congo red injected intravenously on the preceding day. The iodin-sulphuric acid test showed large bluish blotches of amyloid substance in the liver, spleen, adrenals and kidneys. Practically all of the renal glomeruli were infiltrated with amyloid substance. The spleen and liver showed generalized amyloid infiltration. Deposits of amyloid in the adrenals were limited to the cortices. The right knee joint contained clear, slightly turbid, sterile fluid. There was hypertrophy of the synovial membrane with atrophy of the cartilage on the femoral and tibial surfaces. Here and there were projections of bone suggesting hypertrophic changes. Section of the adjacent bone showed thinning out due to atrophy. The right shoulder joint cavity was largely obliterated by bony ankylosis. No cartilage could be recognized, the whole area was atrophic. The bone adjacent to the joint was thin and could be broken with the fingers.

Comment. This evidently was a patient with chronic rheumatoid or infectious arthritis to whom at least 41 injections of vaccine were given at more or less regular intervals over a period of 22 months. The number and spacing of the injections corresponded generally to those given to animals in which amyloid disease developed in a high percentage of cases. Arndt and others noted in horses that amyloid substance appeared between 8 and 16 months after the first injection of vaccine. The question was raised as to whether the arthritis itself, the vaccine therapy, or a combination of the

two was responsible for the development of amyloidosis in the present case. Because of the rarity of reports[12] of amyloid disease associated with a disease as common as arthritis and the regularity with which parenteral injections of a variety of substances produces amyloidosis experimentally, it would seem that the long-continued vaccine therapy was at least an important factor if not the actual cause in its development. The possibility of amyloidosis as a sequela to parenteral shock therapy was suggested by Letterer.[10] Doubrow,[13] in discussing a paper regarding amyloid disease in a tuberculous patient who had received gold injections, also suggested the possibility of a relationship between the therapy and amyloid disease. As far as we are aware, however, the case described here is the first reported in which evidence points strongly to prolonged vaccine therapy as a cause of amyloid disease.

Although recognized amyloidosis seems to be a rare sequela of vaccine therapy it is important to bear the possibility of its occurrence in mind and to discontinue injections upon the appearance of the first evidence of the disease. It is known that amyloid substance produced experimentally may be resorbed if the cause is removed before the disease is too far advanced.[2,14] Furthermore, numerous recorded cases of recovery from amyloid disease[15] indicate that the disease is not always fatal, provided the cause be removed in time.

Summary. A patient suffering from chronic arthritis was given 41 injections of vaccine over a period of 22 months. During this treatment amyloid disease developed and the patient died. Because of the rarity of the occurrence of amyloid disease in chronic arthritis and the frequency with which it occurs following long-continued parenteral injection of numerous substances including vaccine, it was believed that vaccine therapy was responsible for amyloidosis in this case, the first that we know of to be so described.

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THE INFLUENCE OF MUSCULAR ACTIVITY ON PHYSIOLOGIC LEUKOCYTOSIS.

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Blood leukocytes are part of the vast migratory cell population of the body. Their increase during infection is well known. There are also less extreme but nevertheless definite hour to hour variations, termed physiologic leukocytosis. Many investigators have correlated these variations with environmental changes, with various phases of metabolism and with psychic activity. The sources of the extra white blood cells also have been investigated and the pathways by which they are mobilized.

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The experiments reported in this paper are concerned chiefly with the difference in the effect of motion and emotion in rapid leukocyte mobilization, and are grouped as follows: 1, Combined excitement and muscular effort; 2, excitement alone; 3, effect of anesthetics on white blood cells; 4, muscular effort without excitement (under anesthesia); 5, the effects of exposure to cold.

Materials and Methods. Cats were chosen because they are easily aroused to excitement, a generalized sympathetic discharge can be clearly demonstrated, and their blood picture is comparable to that of humans. Over 50 experiments were performed on 21 clinically normal animals.

A standard hemacytometer (Thomas) and diluting pipettes all passed by the United States Bureau of Standards were used.

Blood films were made on slides and stained by Wright's method. Two hundred cells were counted on each slide, counting from edge to edge of the slide. The large and small lymphocytes and mononuclears were all classed as round cells, without further differentiation.

The blood samples were obtained from a marginal vein of the ear, following incision with a sharp knife. All blood samples were taken from a freely flowing drop. Samples were in all cases counted by the person who took them. Usually they were done by one of us; all differential counts were done by one man (C. J. L.).

Variations in total count of less than 1000 cells were regarded as within the limits of experimental error, and therefore insignificant.

A complete experiment usually continued for 1 to 6 hours (average 3 hours) during which time from 3 to 13 samples were taken. The number of samples depended upon the information desired and the type of experiment.

The anesthetics used were ether, given by the open cone method, and sodium amytal (Lilly) administered intramuscularly. The usual dose of amytal was 70 mg. per kilo of body weight.

Excitement with muscular work was obtained by tying the animal on an operating board and allowing it to struggle.

Passive exercise under anesthesia was obtained by supporting the animal on a specially designed constant-speed electric treadmill made by Mr. Victor Phillips in the Department of Anatomy machine shop.

Excitement without muscular work was obtained by riding the animal in a high-speed elevator. All of the animals showed fear, evidenced by crying, dilatation of pupils, and erection of hair. They were placed on the floor of the car without restraint and only those which remained motionless were classified under this category. Observations on those which showed any muscular response, or which tried to escape, were discarded or included under the heading of excitement plus muscular work. The minimal muscular response is a point of importance, which will be emphasized elsewhere.

The experiments listed here are those in which the total count sequences are complete and which have been carefully checked. Many incomplete observations have been omitted for the sake of brevity, but the results are essentially the same as those reported.

Results. *Effect of Muscular Work During Excitement.* Excitement induced responses which varied from mere restless moving around to violent struggling. There were 9 experiments on 6 animals. The total white count rose in all cases. Of these, one was insignificant, and another was discarded because a large number of circulating normoblasts vitiated the counts. The elevations in

total count varied from 5% to 30% with an average rise of 22.7% in 17 minutes. The rise was purely mononuclear in type in 3 cases, mononuclear and neutrophil in 2 cases, pure neutrophil in 1 case, not determined in 3 cases. Excitement with muscular activity increases the total white cell count.

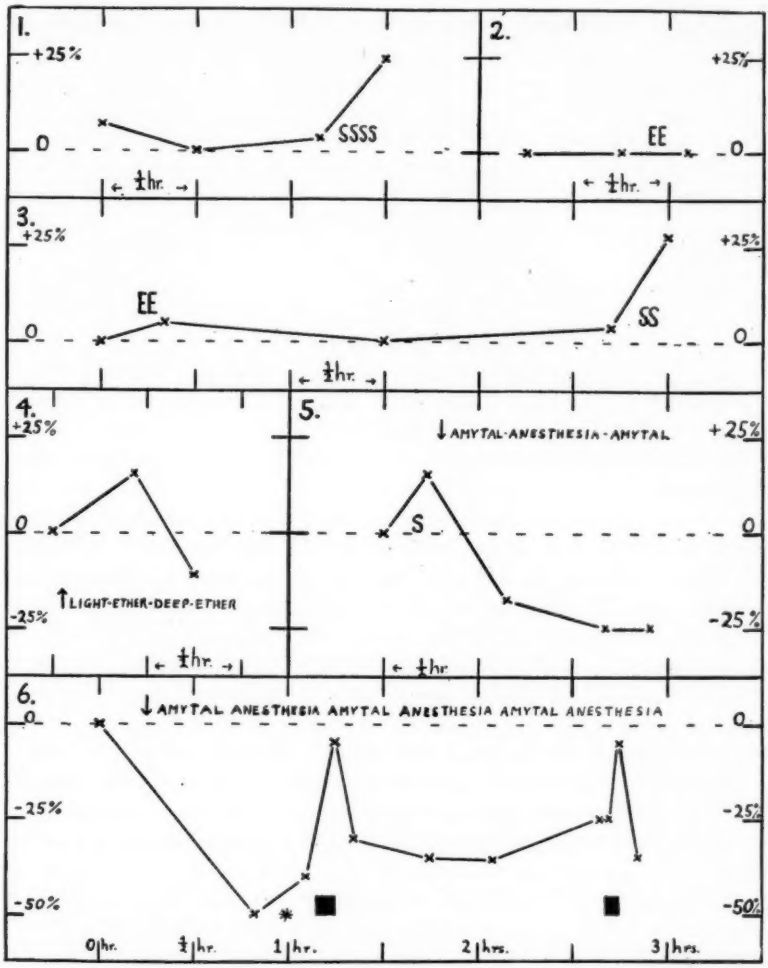
Effect of Excitement Without Muscular Work. Three experiments on 2 animals showed no significant immediate or delayed change in the white cell count following 10 minutes excitement. The small number of satisfactory observations was due to the difficulty in obtaining emotional reactions in the animals without accompanying muscular activity.

Effect of Ether Anesthesia. In 11 experiments on 6 animals, ether anesthesia for 15 minutes caused a significant rise in 7 cases. The lowest rise was 10.0%, the highest 113%; the average 35.28%. Two cases were insignificant. There was one drop of 28%. The effect of prolonged anesthesia was studied in 7 experiments on 4 animals. A complete experiment including initial and postanesthesia counts lasted from $1\frac{1}{2}$ to $3\frac{3}{4}$ hours. The average time necessary to induce anesthesia was 12.5 minutes. There was an initial leukocyte rise in 6 out of 7 cases. Anesthesia was then continued for periods varying from 20 to 55 minutes. The total counts rose further in 3 cases, and dropped in 3 others. One case died from an overdose of ether. The number of minutes' exposure to ether had no apparent tendency to cause either a rise or a fall of the white blood cells, but the depth of anesthesia seemed to be a factor. Because of the initial rise, ether was discarded in our tests for the effects of passive exercise.

Effect of Amytal Anesthesia. In 13 experiments on 9 animals, sodium amytal in anesthetic doses caused a fall of the total white cell count in all cases. This generally occurred within 30 minutes and persisted for 4 to 5 hours. The smallest drop was 5%, the greatest 75%, the average 36.2%. Rises obtained after passive exercise under amytal were considered significant and due to the muscular work.

Effect of Passive Exercise Under Anesthesia. Of 9 observations on 4 animals, 7 showed definite elevation of leukocytes. These ranged from 11% to 50% in 3 to 10 minutes with an average rise of 29.2% in $8\frac{1}{2}$ minutes. The changes in cell types were entirely mononuclear in 2 cases, mononuclear with some neutrophil rise in 4 cases, and a neutrophil rise in 1 case. There was one drop in the total count of 27%, and one insignificant rise. A poly- and a mononuclear decrease occurred in the 1 case of leukopenia. The nature of the insignificant rise was not determined. In this group a complete experiment lasted from 2 to 6 hours.

Exposure to 0° *C.* In 9 experiments, 7 animals were exposed to cold for 15 to 120 minutes. The total count rose in 2 and fell in 3



Graph I. Changes in total blood leukocyte counts under various experimental conditions.

FIG. 1.—After about an hour's quiet, the animal was made to struggle for 15 minutes.

FIG. 2.—Excitement of a fast elevator ride failed to increase the total leukocyte count.

FIG. 3.—Same as Fig. 2, but the count increased when later muscular effort was added.

FIG. 4.—Ether administration was accompanied by a rise during light and a fall during deep anesthesia.

FIG. 5.—A moderate rise as a result of slight struggle was followed by a leukopenia as an injection of amytal began to take effect.

FIG. 6.—The low leukocyte count under amytal is modified by handling the animal in putting it on the machine. A brisk run increased the count, which fell again 5 minutes after cessation of exercise. A second similar run indicated that the rise was present after 3 but not 2 minutes of induced running.

S = Struggle
EE = Elevator excitement
↑ = Beginning of anesthesia
* = Animal put on machine
■ = Passive exercise
0 = Basal count when cat is resting quietly

cases. In the other 4 experiments the changes were insignificant. Cold affected the total count in a variable manner.

Discussion. Our results are in agreement with others in regard to the effect of muscular work. In the experimental animals, passive muscular work under anesthesia caused a rapid increase in white blood cells, which in a majority of the cases was due chiefly to mononuclear cells. The rise in the total count occurred within 5 minutes of onset of exercise, persisted throughout its duration and dropped rapidly toward normal following cessation of work.

Marked variations in the blood count of normal individuals after various forms of muscular work were noted as early as 1903 by Hawk. Since then others (Hasselbalch and Heyerdahl, 1908; Grawitz, 1910; Hochstetter, 1910; Ellermann and Erlandsen, 1911; Garry and Butler, 1929) have also observed a change in the number of leukocytes with a change in posture. They attribute the increase to circulatory shifts with liberation of leukocytes trapped in unused capillaries.

It seems probable that the main factor in the rapid production of leukocytosis following exercise is the dilatation of collapsed capillaries. With the muscles at rest there are vast numbers of inactive vessels holding on their walls many white blood cells. With activity these capillaries open, the cells are swept into the circulation and raise the total count.

The possibility of autonomic nervous control of leukocytosis and leukopenia has been suggested by Camus and Pagniez (1908), Mora, Amtman and Hoffman (1926) and Menkin (1928).

The effect of combined emotional and muscular stimulus does not differ appreciably in our experiments from that of muscular work alone, and we were unable to show any increase in white blood cell count from emotional stimulus in the absence of muscular work. We believe that the effects obtained by others and ascribed to emotion are due to a combination of motion and emotion, with major effects by motion. In a few of our cases the animals remained perfectly quiet and not under restraint, although sympathetic stimulus was evidenced by erection of the hair and dilatation of the pupils. No increase in leukocytes occurred. Our failure to obtain a leukocyte rise with excitement alone may be due to a limited circulatory adjustment in the absence of muscular response to the emotional stimulus.

We believe that during excitement with activity the circulation changes resulting in leukocytosis may be due to a reflex and not a generalized sympathetic discharge. The reflex would be induced by the need for blood in the active tissues (skeletal muscle). If a strong, generalized sympathetic discharge without accompanying muscular activity could be obtained, one might get a purely emotional leukocytosis. This is suggested by the results obtained with injections of adrenalin (Camus and Pagniez, 1908). The muscular activity factor will, however, be a difficult one to rule out.

The period of excitation during ether anesthesia in our animals was accompanied by a rise of the total white count. This rise can be explained by the excessive activity of the animals. The total count dropped during very deep anesthesia, but rose again during the recovery phase.

The leukopenia during amytal anesthesia makes the rises following passive exercise doubly significant in those cases.

The differences encountered in animals exposed to cold may also be explained by their relative activity. Our experiments were conducted in a small darkened refrigerator in which the animals generally remained quiet. Furthermore, exposure to cold while the animal was under ether anesthesia caused a leukopenia. In experiments by Zwemer and Lyons (1928), cats were subjected to cold in a large well-lighted refrigerating room, in which considerable activity was possible. An increase in total counts occurred in their cases, except in those animals that had had their sympathetic nervous system removed.

Other types of physiologic leukocytosis have been described (Rous 1908, Scheider and Havens 1915, Becher 1918). Although some of them are undoubtedly contributory factors, their speed of reaction is probably too slow to account for the rapid rises encountered in the experiments reported in this paper.

The rhythmic basal changes in normal human subjects (Japha, 1900; Galambos, 1912; Sabin, Cunningham, Doan and Kindwall, 1925) also differ in their time relationships from our experimental results.

Summary. 1. Emotional stimulus with muscular activity was followed by a leukocytosis. This was generally mononuclear in type.

2. Emotional stimulus alone in our few cases effected no significant variation of total white count.

3. Passive work under anesthesia raised the total white cell count, the rise being similar to that induced by excitement plus activity.

4. The rapid increase following muscular work is probably due to a dilatation of unused muscle capillaries, the entrapped leukocytes being swept into the general circulation.

5. Sodium amytal (intramuscularly in anesthetic doses) caused a constant leukopenia.

6. Ether anesthesia was characterized by an initial leukocytosis, the elevation being evidenced by all cell types. Deep anesthesia was accompanied by a drop in the total count. These effects may be correlated with the initial hyperactivity and subsequent relaxation of the animal.

7. Exposure to cold (0° C.) produced no constant change in the total white count.

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THE SCHILLING COUNT IN 59 CASES OF CHRONIC ARTHRITIS WITH A CORRELATED SEDIMENTATION RATE IN 30 CASES.

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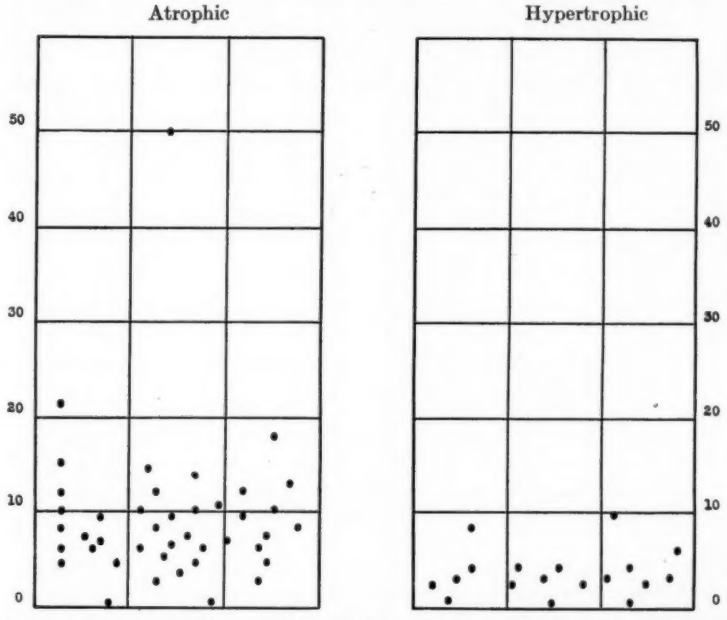
The system of differentiation of the white blood cell count as developed by Schilling in 1911 has proved to be of much value in the diagnosis, prognosis and treatment of disease. The voluminous literature on the subject certifies this fact. Crocker and Valentine,[1] after a careful and very interesting analysis of 6000 Schilling hemograms, state that the method is most practical and scientific. And yet a careful study of the literature on chronic arthritis reveals very little study as regards the Schilling count in this chronic disease. Also there have been extensive studies of the sedimentation rate in joint disease, but, as far as I know, no one has attempted a correlated study of the younger neutrophils and the sedimentation

rate. The opinion cited by Oppel[2] and his co-workers, that an isolated observation of the sedimentation rate is of little value in differentiating various forms of arthritis, is to be seriously considered.

The author has studied 59 cases of chronic arthritis with particular emphasis of the Schilling differential as a means of differentiating the two main types of chronic arthritis. He also has correlated this study with sedimentation determinations by the method described by Rourke and Ernstene[3] in 30 cases. That there is a definite correlation between the Schilling count and the sedimentation rate is well demonstrated by a study of Charts I and II. In atrophic

CHART I.—THE SCHILLING COUNT IN 59 CASES OF CHRONIC ARTHRITIS.



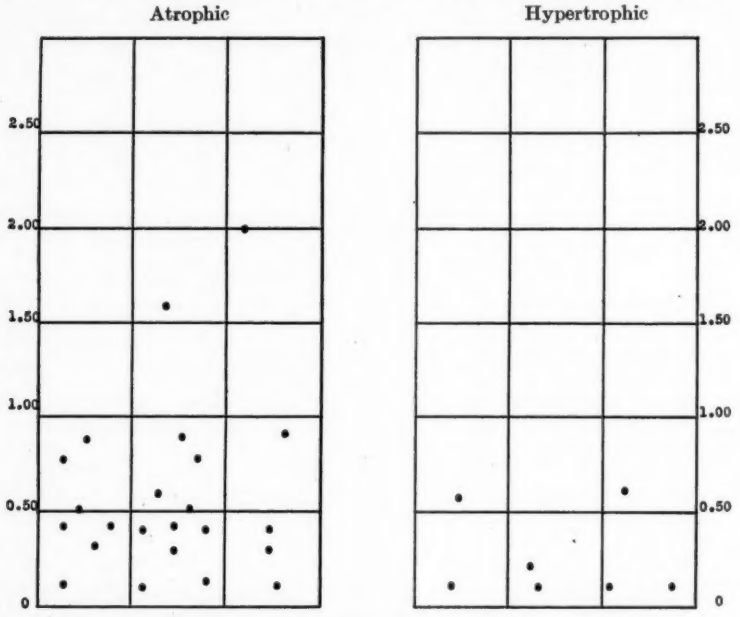
Note that most cases of atrophic arthritis are above 4%, whereas most cases of hypertrophic arthritis are 4% or below. (Scale is in per cent of younger neutrophils —myelocytes, juveniles and stabnuclears combined.)

arthritis the percentage of the younger neutrophils is increased over the normal in most cases, whereas, in hypertrophic arthritis these cells are usually not increased. The sedimentation rate, in general, follows the same general trend. However, it is evident that many of the cases of atrophic arthritis show an upper level of normal sedimentation rate (normal index is 0.8 to 0.35).

Table 1 includes 42 cases of atrophic arthritis. In this group, the Schilling was shifted to the left in 33 cases (78%). Four of the 9 cases in which the Schilling was not shifted to the left showed the upper limit of the normal younger polys. That the stage of the

disease in which the Schilling count is done is important is demonstrated by G. D. During the acute phase of the arthritis there were 12% of the younger neutrophils present in the blood smear, whereas, during the resting stage in the same case there were only 3% of these cells present.

CHART II.—THE SEDIMENTATION RATE IN 30 CASES OF CHRONIC ARTHRITIS.



Note that most cases of atrophic arthritis are above 0.35, whereas, most cases of hypertrophic arthritis are below 0.35. (Scale in mm. per minute.)

Table 2 includes 17 cases of hypertrophic arthritis. In this group the Schilling was shifted to the left on only 3 cases (17%). Of these 3 cases the highest percentage of cells younger than the stabnuclear stage was 2% juveniles, whereas, in the atrophic group we find 12% juveniles in 1 case and in another we even find 2% myelocytes.

In the correlated study there is agreement of the Schilling count and the sedimentation rate in 22 instances and disagreement in 8 cases. By "agreement" the author means that both the sedimentation rate is diminished in time and the Schilling is shifted to the left. The shifting of the Schilling to the left and a normal sedimentation rate, or a normal Schilling differential with a sedimentation rate which is decreased in time, is called "disagreement" in this paper. In 29 instances the Schilling count substantiates the clinical diagnosis and fails to do so in only 1 case. The sedimentation rate substantiates the clinical diagnosis in 22 cases and does not in 8 instances. From this preliminary correlated study it would seem that

the Schilling count is more valuable than the sedimentation rate in differentiating the two main types of chronic arthritis.

TABLE 1.—SCHILLING DIFFERENTIALS IN 59 CASES OF CHRONIC ARTHRITIS WITH A CORRELATED SEDIMENTATION RATE IN 30 CASES.
(ATROPHIC ARTHRITIS.)

	My. %	Juv. %	Stabs. %	Segs. %	Lyms. %	Monos. %	Eos. %	Bas. %	Sed. time.
L. McN.	..	12	38	32	14	3			
I. C.	2	3	16	40	30	5	2	2	0.80
M. M.	..	3	15	45	30	3	4	..	0.70
M. C.	..	..	15	44	34	5	..	2	0.59
S. Z.	..	..	14	54	27	5	..	..	0.80
H. H.	1	3	9	39	41	3	4	..	2.00
E. S.	..	2	11	55	26	2	4	..	1.55
G. D. (acute stage)	1	2	9	41	40	..	6	1	
T. C.	..	2	10	47	39	..	2	..	0.43
C. P.	..	1	11	72	16				
G. H.	..	..	11	27	57	3	2		
A. G.	..	3	7	69	15	4	2		
C. G.	..	1	9	50	37	1	2	..	0.80
B. M.	..	1	9	58	26	3	3		
R. M.	..	..	10	63	23	3	..	..	0.10
E. L.	..	..	9	57	25	6	3		
R. H.	..	..	9	62	24	5	..	..	0.20
M. R.	..	..	9	69	20	1	1		
G. B.	..	2	6	67	21	..	4	..	0.38
M. B.	..	..	8	65	22	5			
C. M., combined (atrophic predominating)	..	..	8	46	39	5	2	..	0.15
A. M.	..	2	5	33	50	..	2	1	
A. V.	..	..	7	72	18	3			
M. DeL.	..	..	7	49	41	3	..	..	0.50
F. H., combined (atrophic predominating)	..	..	7	42	47	2	2	..	0.10
H. A.	..	..	7	53	22	5	3	..	0.75
V. M.	..	..	6	78	26				
J. F.	..	..	6	71	18	1	4	..	0.50
L. DeM.	..	..	6	68	23	..	3	..	0.38
H. W.	..	..	6	42	48	4	..	..	0.30
C. F.	..	..	6	59	31	2	2	..	0.40
A. W.	..	..	6	68	24	2	..	..	0.39
J. M.	..	..	5	75	17	1	2		
L. T.	..	..	4	67	25	3	1		
A. N.	..	..	4	60	33	1	2	..	0.35
E. W.	..	..	4	71	16	6	3		
B. R.	..	..	4	79	12	5			
G. D. (resting stage)	..	..	3	67	25	1	4		
M. K.	..	..	3	52	39	5	1		
D. K.	..	..	2	35	60	2	1	..	0.40
H. P.	..	..	2	64	19	10	3	1	
G. H.	..	..	..	68	29	3			
C. B.	..	..	..	50	50				

Another interesting observation from the correlated study is that in all instances in which the stabnuclear count is above 10% and in

all cases in which we find younger neutrophils than the stab state, the sedimentation rate is more rapid than normal. In all such cases the author has always encountered the atrophic type of arthritis. This fact is well demonstrated by a study of the tables. In only 1 case of atrophic arthritis (A. N.) do we find both a normal Schilling differential and a normal sedimentation rate and in this case both values are the upper limit of normal. Furthermore, this was a "burnt out" case of atrophic arthritis.

TABLE 2.—SCHILLING DIFFERENTIALS IN 59 CASES OF CHRONIC ARTHRITIS WITH A CORRELATED SEDIMENTATION RATE IN 30 CASES.
(HYPERTROPHIC ARTHRITIS.)

	My. %	Juv. %	Stabs. %	Segs. %	Lyms. %	Monos %	Eos. %	Bas %.	Sed. time.
J. Q. (Mixed arthritis, hypertrophic predominating)	..	2	7	52	34	2	3		
W. B. (acute knee joint)	..	1	7	38	56	3	5		
L. N.	..	..	6	70	22	..	2		
N. W.	..	..	4	64	22	8	2	..	0.65
C. B.	..	..	4	68	27	1	..	..	0.20
A. F.	..	..	4	42	44	2	8	..	0.21
G. R.	..	..	3	61	33	1	2	..	0.60
C. S.	..	..	3	64	29	2	2	..	0.15
R. B.	..	..	3	45	37	7	8		
C. G.	..	..	3	73	24				
S. S.	..	..	2	68	25	..	2	1	0.27
F. W.	..	..	2	45	47	2	3	..	0.23
E. B.	..	..	2	56	40	..	2	..	0.31
G. S.	..	..	2	66	30	..	2		
J. M.	..	..	..	68	36	6			
C. A.	..	..	..	68	26	6			
N. P.	..	..	..	68	26	5	1		

From this preliminary study it would seem that the Schilling count is of value in differentiating the two main types of chronic arthritis. The sedimentation rate as described by Rourke and Ernstene, together with a Schilling differential, increase the accuracy with which this differential study may be made. Only in 4.7% of the total cases of atrophic arthritis did the author obtain both a normal Schilling count and a normal sedimentation rate. The practical application of this study in the treatment of chronic arthritis will be discussed in a future article.

Summary. 1. Schilling studies in 59 cases of chronic arthritis are presented.

2. Thirty cases of chronic arthritis with both Schilling differentials and sedimentation rates are discussed.

3. The Schilling count is of value in differentiating atrophic from hypertrophic arthritis.

4. Correlated studies of the Schilling count and the sedimentation rate seem to increase the accuracy with which this differential study can be made.

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INCIDENCE OF INFECTION WITH INTESTINAL PROTOZOA IN MINNESOTA.

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Craig[1] has estimated that between 5% and 10% of the population of the United States are carriers of Endamœba histolytica. It is well known that a higher percentage of infestation occurs in warm climates and under crowded living conditions.[2,3] Kofoid and Swezy[4] found E. histolytica present in the stools of 67% of 91 soldiers examined who had recently returned from overseas duty in the World War. Meleney, Bishop and Leathers[5] reported 11.4% infestation in the rural districts of Tennessee. In a survey carried out by Andrews and Paulson[6] in 1931, however, E. histolytica was found in only 0.3% of 312 individuals who were living under normal home conditions in Baltimore. And more recently Hinshaw and Showers,[7] working in Philadelphia, found 1.1% of 368 unselected hospital patients positive when examined. Riley,[8] in 1929, examined a selected group of approximately 500 ex-service men in Minnesota and found 1.4% infected with E. histolytica. He concluded "that E. histolytica is distinctly less common in the north central states than might be inferred from current statistics."

Dobell[9] has estimated that about one-third of the actual E. histolytica infections will be discovered by a single examination. Carter and coworkers[10] found on the first examination 33.4% of the total number of infections with E. histolytica which were found on 6 examinations. Kessel and Svensson,[11] in Peking, report the following percentages of the total infections which were found on the first examination in a series of 6 examinations: E. histolytica, 44%; E. coli, 47%; E. nana, 47%; Iodamœba, 30%; Chilomastix, 29%; Giardia, 42%.

In examining stools for intestinal protozoa, Magath and Ward[12] prefer the study of a fresh preparation of liquid stools obtained

after a saline purge to any other single method. Spector,[13] in 1932, concluded "in the detection of E. histolytica infections, cultural methods are probably superior to direct fecal examination."

The present investigation was carried out to ascertain the presence of E. histolytica carriers among the healthy working food handlers of a large railway system, a single* examination was made, except in positive cases, when a second specimen was included. The following results are the actual findings without calculations as to the probable percentage of infection; 146 apparently normal working employees were examined. None of this number gave a history of past infection with E. histolytica.

Material and Methods. The examinations were made upon fresh stools passed at the laboratory after the administration of a saline cathartic. The examination consisted of:

1. Immediate examination of a fresh preparation using a warm stage to guard against loss of temperature.
2. Examination of a portion of the stool emulsified in 1% I in 2% KI, as recommended by Craig.
3. Culture of the stool on Cleveland's[14] media. This was incubated 24 hours at 37° C., and a portion searched on the warm stage for motile forms.

Results. In the detection of E. histolytica there was complete agreement between the cultural and direct examination methods. That is, none of the stool cultures showed the presence of E. histolytica except those in which E. histolytica had been found in the fresh stool by direct examination.

The per cent infestation with other protozoan parasites reported is compiled from the findings of the fresh preparation and iodin stain methods. The following table shows the incidence of infestation with protozoan intestinal parasites in a series of 146 apparently normal working individuals.

TABLE 1.—INCIDENCE OF INTESTINAL PROTOZOA.

Organisms.	No. of cases.	Per cent.
E. histolytica alone	0	0
E. histolytica and B. hominis	1	0.68+
E. histolytica and B. hominis and E. nana	1	0.68+
E. coli alone	1	0.68+
E. coli and B. hominis	6	4.11
E. coli and B. hominis and Iodamœba bütschlii	1	0.68+
Endolimax nana alone	3	2.0
Endolimax nana and B. hominis	9	6.16
Endolimax nana and I. bütschlii	1	0.68+
Endolimax nana and B. hominis and C. mesnili	1	0.68+
Iodamœba bütschlii alone	1	0.68+
Iodamœba bütschlii and B. hominis	1	0.68+
Giardia intestinales alone	1	0.68+
Giardia intestinales and B. hominis	1	0.68+
Chilomastix mesnili alone	0	0
Chilomastix mesnili and B. hominis	2	1.37
Trichomonas hominis alone	1	0.68
Trichomonas hominis and B. hominis	1	0.68
Blastocystis hominis alone	54	37.0

* Before additional examinations could be made the order authorizing the survey was rescinded.

TABLE 2.—TOTAL INCIDENCE.

Organisms.	No. of cases.	Per cent.
E. histolytica	2	1.37
E. coli	8	5.50
E. nana	15	10.27
I. bütschlii	4	2.74
G. intestinales	2	1.37
C. mesnili	3	2.05
T. hominis	2	1.37
B. hominis	78	53.42
Negative	60	41.10

Discussion. Of the 146 individuals whose stools were examined, the stools of 24.67% were found to contain at least one of the intestinal parasites other than B. hominis. Since the significance of B. hominis is at present somewhat undetermined it has been included in this study. Blastocystis hominis was present in the stools of 37% of the individuals, unaccompanied by any other parasite. Forty-one per cent of the stools were found to contain no protozoan parasite.

Since this investigation embraces an unselected group of working and apparently healthy individuals, it serves to show that a small percentage of the normal population in the north central United States are carriers of E. histolytica. However, this percentage of carriers is not as great as the 5 to 10% which Craig has estimated for the entire United States. Nevertheless, with the increasing facility of travel, the low percentage of 1.37 reported might well reach a higher level within a few years.

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THE HETEROPHIL ANTIBODY TEST IN LEUKEMIA AND LEUKEMOID CONDITIONS.*

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This study is an attempt to confirm the original observation of Bernstein (1934) that in leukemia the heterophil antibody titre is uniformly at a low level, and to investigate heterophil antibody formation in leukemia and certain leukemoid conditions before and after the parenteral administration of horse serum. A heterophil antibody is an antibody group possessing the capacity to react with antigens, different from and phylogenetically unrelated to the specific antigen instrumental in producing the antibody response.

Method. The method used in this study is similar to that employed by Davidsohn (1929, 1930), Paul and Bunnell (1932), Bunnell (1933), and Bernstein (1934). The following materials are employed: Serum of the patient, a 2% suspension of washed sheep red cells, and physiologic saline solution. The serum is inactivated at 56° C. for 15 minutes, and diluted in physiologic saline in a series ranging from undiluted serum to a dilution of 1 to 16, or as far as is indicated. To each tube containing 0.5 cc. of diluted serum, 0.5 cc. of a 2% solution of washed sheep red cells is added and finally the addition of 1 cc. of physiologic saline brings the total volume to 2 cc. The tubes are shaken, placed in a water bath at 37° C. for 1 hour and kept overnight in the ice box. The next morning the tubes are inverted 3 times and the degree of sheep cell agglutination is recorded as follows:

+++ single mass of cells; ++ large flakes; + fine flakes; 0 no agglutination.

To facilitate comparison with the results of previous workers, the serum dilutions are expressed in terms of the proportion of serum to saline present in the original 0.5 cc. added and *not* with reference to final serum dilution, *i. e.*, "undiluted" is actually 1 to 4, a 1 to 1 dilution is 1 to 8, and so forth.

* Presented before Section on General Medicine, College of Physicians, Philadelphia, December 18, 1934.

Previous workers have found, in normal individuals and in patients suffering from a variety of diseases with the exception of infectious mononucleosis and serum sickness, that sheep cell agglutinins may be present up to a serum dilution of 1 to 16. Bernstein (1934) for purposes of convenience, designated the range of serum dilutions below 1 to 4 as Zone 1, the interval between 1 to 4 and 1 to 16 as Zone 2, and the distribution above 1 to 16 as Zone 3. Bernstein (1934) found that in over 300 cases other than serum sickness or infectious mononucleosis, 30% fell in Zone 1 and 70% in Zone 2. Similarly Bunnell (1933) in over 1600 cases found that 40% fell in Zone 1 and 60% fell in Zone 2. Stuart *et al.* (1934) found that in 300 cases 26% fell in Zone 1 and 74% in Zone 2. In a series of 100 hospital cases unselected except to exclude serum sickness, infectious mononucleosis and leukemia, we found that 36% fell in Zone 1 and 64% fell in Zone 2, and no case fell in Zone 3. Thus it seems safe to assume that normal individuals and those suffering from a variety of diseases other than serum sickness and infectious mononucleosis all exhibit a heterophil antibody titre of less than Zone 3 magnitude. Furthermore, of this group at least 60% fall in Zone 2.

TABLE 1.—LOW HETEROPHIL ANTIBODY RANGE IN LEUKEMIA.

Case No.	Diagnosis.	Zone 1.			Zone 2.	White blood cells, range.	
		Undil.	1 to 1.	1 to 2.	1 to 4.		
1	Acute lymphatic leukemia	+	+	−	−	22,000	
2	Chronic lymphatic leukemia	−	−	−	−	53,800	22,000
3	" " "	−	−	−	−	98,200	11,000
4	" " "	−	−	−	−	38,000	27,000
5	" " "	−	−	−	−	21,800	106,000
6	" " "	+	−	−	−	4,200	8,600
7	Acute myelogenous leukemia	−	−	−	−	14,000	
8	" " "	+++	+++	+++	++	42,000	
9	Chronic " "	−	−	−	−	420,000	9,000
10	" " "	+	−	−	−	9,200	22,400
11	" " "	+	−	−	−	188,000	64,000
12	" " "	−	−	−	−	20,000	137,000
13	" " "	++	+	−	−	14,000	68,000
14	" " "	+	−	−	−	90,000	11,200
15	" " "	++	+	−	−	20,000	320,000
16	" " "	−	−	−	−	82,000	
17	Subleukemic myel. leukemia	+	−	−	−	2,600	9,400

Seventeen cases of leukemia were studied—1 of acute lymphatic leukemia, 5 of chronic lymphatic leukemia, 9 of chronic myelogenous leukemia and 2 of acute myelogenous leukemia. In all these cases the heterophil antibody titre fell in Zone 1 and in no instance could heterophil antibody be demonstrated above a serum dilution of 1 to 1 —except in a single case of acute myelogenous leukemia who had received 28 transfusions. These results confirm the previous work

of Bernstein (1934), who reported that 20 of 21 cases of leukemia had a heterophil titre that fell in Zone 1.

This finding of a low heterophil antibody content in the serum of patients with leukemia was not influenced by the level of the leukocyte count, or by the predominating cell present, and was obtained irrespective of whether or not the patient had received radiation therapy. It was also noted that a tremendous shift of the blood picture from that of florid leukemia to a strictly aleukemic phase did not influence this constantly low heterophil antibody level.

We also found in a study of 5 cases of proven lymphosarcoma and 3 cases of Hodgkin's disease, a constantly low titre of heterophil antibody, all falling in Zone 1.

We conclude from these observations that with heterophil antibodies distributed in Zone 2 or Zone 3, one may with some assurance rule out leukemia. However, if the heterophil antibody titre falls in Zone 1, the patient may or may not have leukemia. The heterophil antibody test up to this point is therefore of value only in establishing *negative* evidence concerning the diagnosis of leukemia.

Previous workers have shown that specific antibody formation in leukemia is disturbed. Moreschi (1914) was able to demonstrate little or no specific agglutinin formation after the injection of typhoid vaccine in 6 cases of chronic myelogenous leukemia and 2 cases of chronic lymphatic leukemia. Rotky (1914) using a harmless vibrio cultivated from water was able to demonstrate specific agglutinin formation in 8 control cases, but could not demonstrate any agglutinin formation in 2 cases of leukemia (1 chronic myelogenous and the other chronic lymphatic).

Davidsohn (1929) first reported that following the administration of horse serum there was an increase in *heterophil* antibody titre. He later reported (1933) a series of heterophil titres in cases receiving immune sera for therapeutic purposes. The average titre for the control group was a serum dilution of 1 to 6, the average titre for the group receiving serum but in whom serum sickness did not develop was a serum dilution of 1 to 18 and in the group developing serum sickness, the average heterophil titre was a serum dilution of 1 to 63. Bernstein (1934) found an increase in the heterophil antibody titre in 11 cases receiving various immune sera. In our study the heterophil antibody titre in 14 non-leukemic cases which had received various immune sera was found to be in the serum dilution range of Zone 3, thus confirming the work of these investigators.

Bernstein (1934) injected horse serum intravenously in a case of chronic lymphatic leukemia and could demonstrate no increase in heterophil antibody content of the serum. A second case of probable leukosarcoma showed a minimal rise in heterophil antibody titre after the parenteral administration of horse serum. Neither of these cases developed evidence of a serum reaction.

This finding in leukemics contrasts sharply with Davidsohn's (1933) demonstration of a constant increase in heterophil antibody titre after parenteral administration of horse serum in non-leukemics regardless of whether or not serum sickness occurred. This suggests the possibility that in leukemic individuals the mechanism of heterophil antibody formation may be inhibited or deficient just as the mechanism of specific antibody formation is deficient.

The evidence thus far suggests that normal individuals and those suffering from a variety of disorders show a rise in heterophil antibody titre from Zone 1 (40% of total group) or Zone 2 (60% of total group) to Zone 3 when given horse serum parenterally, whereas the few leukemics previously tested (all in Zone 1) show no significant rise of heterophil antibody titre after the administration of horse serum. This difference in response to horse serum might seem to offer a positive means of establishing the diagnosis of leukemia.

TABLE 2.—HETEROPHIL ANTIBODIES IN LEUKEMICS BEFORE AND AFTER RECEIVING HORSE SERUM.

Case.	Clinical diagnosis.	Biopsy.	Type.	Undil.	1 to 1.	1 to 2.	1 to 4.	
S.	Chr. lymph. leuk.	Atypical lymph. leuk.	O	− −	− −	− −		− −
D.	Chr. lymph. leuk.		O	− +	− +	− −		− −
D.	Chr. lymph. leuk.	Chr. lymph. leuk.	A	− −	− −	− −		− −
C.	Chr. lymph. leuk.		A	− +	− +	− −		− −
B.	Chr. subleuk. lymph. leuk.	Lymph. leuk.		− ++	− +	− −		− −
H.	Chr. myel. leuk.		B	− +++	− ++	− +		− −
M.	Chr. myel. leuk.		B	+ +++	− +++	− +++	− +++	1 to 64 +
M.	Chr. myel. leuk.		O	++ +++	+ +++	− +++	− +++	1 to 512 +
F.	Chr. aleuk. leuk. *vs.* lymphosarc.	Chr. aleuk. leuk. *vs.* lymphosarcoma	A	+ +	− −	− −	− −	
M.	Aleuk. leuk. *vs.* lymphosarc.	Lymphosarcomatous type of hyperplasia		+ ++	− +	− −	− −	
P.	Hodgkin's dis. *vs.* aleuk. leuk.	Atypical Hodgkin's dis.		+ +++	− ++	− +	− −	
L.	Subleuk. lymph. leuk.	Chr. inflammation		++ +++	+ +++	+ +++	− +++	1 to 32 +
G.	Monocytic leuk.?		O	+ +++	− +++	− +++	− +++	1 to 64 +

The upper titration represents the heterophil antibody titre present before the administration of horse serum. The lower titration represents the highest titre after horse serum injection.

This possibility was investigated in 8 cases of known leukemia and 5 in which the differential diagnosis was in doubt. After

obtaining at least 2 determinations of heterophil titre on separate days, the patient received an intradermal injection of 0.05 cc. of normal horse serum. In the absence of a positive reaction, 5 cc. of horse serum were injected intramuscularly into the buttock. The next day 10 cc. of the serum were injected into the opposite buttock. Blood was withdrawn at frequent intervals following the serum injections and the heterophil titre determined. In several cases the heterophil titre was determined for periods of 6 weeks after serum injection.

This leukemic group was composed of 5 cases of chronic lymphatic leukemia and 3 cases of chronic myelogenous leukemia. We also tested 2 cases in which the diagnosis by biopsy rested between aleukemic leukemia or lymphosarcoma, 1 diagnosed by biopsy as atypical Hodgkin's disease, 1 with generalized lymph node enlargement, a white count of 13,600 and a differential count with 73% lymphocytes diagnosed by biopsy as "hyperplasia of chronic inflammation," and 1 in whom a monocytosis associated with an enlarged spleen raised the possibility of monocytic leukemia.

The 5 cases of chronic lymphatic leukemia had no significant rise in heterophil antibody titre after horse serum injection. In *no* instance did the heterophil titre shift beyond Zone 1.

The 3 cases of chronic myelogenous leukemia, however, had a *marked* change in heterophil antibody titre after the administration of horse serum. In 1 case there was a rise from no agglutination in "undiluted" serum to definite agglutination in a dilution of 1 to 2. In the other 2 cases the agglutinin titre rose from the range of Zone 1 to agglutination in a serum dilution of 1 to 64 in one, and to agglutination in a serum dilution of 1 to 512 in the other. In the last case the agglutinin titre started to rise 5 days after serum injection and 2 days later the patient had a moderately severe attack of serum sickness. None of the other cases of leukemia developed serum sickness.

In the 2 cases in which the diagnosis by biopsy rested between aleukemic leukemia and lymphosarcoma and in the case diagnosed as atypical Hodgkin's disease by biopsy, there was no shift in the agglutinin titre out of the range of Zone 1 after serum administration.

The case of generalized adenopathy with lymphocytosis diagnosed by biopsy as "hyperplasia of chronic inflammation" and the case in which monocytic leukemia was suspected, each exhibited a shift in heterophil antibody from Zone 1 to Zone 3. Both of these individuals recovered completely and follow-up examinations show them to be in good health.

It is evident that in our small series of cases of chronic lymphatic leukemia administration of normal horse serum does not produce an increase in heterophil antibody. On the other hand, the parenteral administration of normal horse serum in the cases of chronic

myelogenous leukemia elicits an increase in heterophil antibody in no wise differing from that produced in non-leukemic individuals. Thus it is apparent that no difference between the non-leukemic and chronic myelogenous leukemia cases can be established on the basis of this procedure.

Our findings indicate that the response of heterophil antibody formation following the parenteral administration of horse serum may possibly be of value in separating cases of lymphatic leukemia, aleukemic lymphatic leukemia, lymphosarcoma, and Hodgkin's disease on the one hand, from normals and from other diseases on the other hand. It is of no value in differentiating between lymphatic leukemia, lymphosarcoma and Hodgkin's disease, which, as far as this evidence goes, seem to be serologically related. It is furthermore obvious that myelogenous leukemia falls within the normal range of response to serum administration and thus diverges sharply, and to us unexpectedly, from the lymphatic leukemia group.

It is of interest to note the results of serum administration in a case of general lymph adenopathy with a white count of 13,600 and a lymphocyte percentage of 73. The clinical diagnosis was chronic lymphatic leukemia in the subleukemic stage. The original heterophil antibody titre fell in Zone 1 and was compatible with the diagnosis of leukemia. However, after serum administration, the heterophil antibody titre rose into the range of Zone 3. This led us to question the diagnosis of leukemia. A subsequent lymph node biopsy revealed "hyperplasia of chronic inflammation" and substantiated the inference drawn on the basis of the rise in heterophil antibody titre, that this case was not lymphatic leukemia. Follow-up study of this case indicates the correctness of this position in as-much as this man is perfectly well.

A heterogenous group of cases was studied with the following findings: Two cases with tuberculous adenitis fell in Zone 2; 5 acute non-specific adenitis cases were distributed in Zones 1 and 2; 1 of secondary lues with generalized adenopathy fell in Zone 1; 5 of polycythemia vera were distributed in Zones 1 and 2; 4 of typhoid fever all still febrile fell in Zone 2; 3 of aplastic anemia fell in Zones 1 and 2; 3 of purpura hemorrhagica (thrombocytopenic) fell in Zones 1 and 2 and single cases of Felty's syndrome, primary pernicious anemia, and pneumonia fell in Zone 1. In sharp contrast to the findings in this heterogenous group, we have found in 10 cases of acute infectious mononucleosis a high titre of heterophil antibody (all in Zone 3). The heterophil antibody titre reached Zone 3 within a few days of the onset in typical cases, and roughly parallels the abnormal lymphocytosis which, however, may be present after the heterophil antibody titre has returned to normal levels. We have found a Zone 3 titre, however, 6 weeks after onset in 1 case and 12 weeks after onset in another. In 3 other cases, after 2 years, 8 months, and 12 weeks respectively, we found that the heterophil antibody titre was present in the normal range.

Conclusions. 1. The heterophil antibody titre in the sera of 16 cases of leukemia was found to be uniformly and repeatedly at a low level (Zone 1) regardless of the stage and type of the disease. One case of acute myelogenous leukemia was found to be in Zone 2. This case, however, had received 28 blood transfusions. This constant finding may be of value in ruling out the diagnosis of leukemia in any case in which a high heterophil antibody titre is found.

2. A low or normal titre of heterophil antibody was found also in 3 cases of Hodgkin's disease, 5 of lymphosarcoma, 5 of polycythemia vera, 4 of agranulocytic angina, and a number of miscellaneous cases including typhoid fever, simple adenitis, syphilis, tuberculosis, anemia, etc.

3. A high titre (Zone 3) was found in serum sickness and acute infectious mononucleosis, thus confirming the reports of Paul, Bunnell, Davidsohn and others.

4. The parenteral administration of horse serum did not produce a rise in the heterophil antibody titre in 5 cases of chronic lymphatic leukemia. This finding is in accord with previous evidence.

5. A similar failure of increase of heterophil antibody titre following horse serum injections was found in 1 case of "atypical" Hodgkin's disease and 2 of lymphosarcoma, suggesting the possibility of a biologic relationship of these conditions to lymphatic leukemia.

6. The parenteral administration of horse serum in 3 cases of chronic myelogenous leukemia produced a marked rise in heterophil antibody titre similar to that occurring in non-leukemic individuals. This finding is not in accord with previous evidence, and suggests the possibility of a real biologic difference between myelogenous leukemia on the one hand, and the lymphatic group on the other hand.

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PERNICIOUS ANEMIA AND MALIGNANT NEUTROPENIA: A CASE REPORT.

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The occurrence of malignant neutropenia (agranulocytosis) as a terminal event in a case of pernicious anemia which was receiving active and adequate treatment seems worth reporting.

Case Report. Mrs. J. S. (No. 18073), American, was seen at her home in consultation on October 22, 1933. Her family, past and marital history were unimportant. She had passed the menopause in the late forties and had had no bleeding or discharge since. Her present illness began indefinitely in the summer or early fall of 1930 with weakness, vague indigestion and intermittent soreness of the tongue. In the early summer of 1933 there was a marked increase in these symptoms and about August she developed numbness and tingling in her hands and feet which gradually spread until at the time she was seen it involved the whole body below the neck. With the development of this numbness she became progressively more awkward until finally she could neither walk, feed nor care for herself nor even button her night dress. There was no involvement of the organic reflexes. For 6 weeks she had been bedfast, her appetite had been very poor and she had had frequent, irregular spells of nausea, vomiting and diarrhea. There has been a moderate though indeterminate loss in weight.

Examination showed a slim, thin, extremely pale, alert woman in the mid-sixties, apparently seriously and chronically ill. The pallor, however, was distinctly yellowish and the conjunctiva were subicteric. Her tongue was smooth and without papillæ and presented two or three hyperemic areas which were sore and tender. Her pupils reacted normally but there was complete absence of all the superficial and deep reflexes and bilateral positive Babinski signs. There was marked disturbance of coördination, sense of position and deep sensation in all the extremities, more marked in the lower. She could not recognize ordinary objects by the sense of touch. Pain sensation was moderately diminished and delayed. The remainder of the examination, including pelvic and rectal, was normal. Examination of the blood revealed hemoglobin, 20 to 25% (Tallqvist); erythrocytes, 1,220,000, and leukocytes, 5000. The stained preparations showed the changes characteristic of a high-grade macrocytic anemia. The differential count was unfortunately lost, but there were about 70% neutrophils, many of which were the multilocular type characteristic of the old forms seen in pernicious anemia.

She was placed upon the anemic diet of Minot and Murphy, given 15 capsules of "Extralin-Lilly" daily, dilute hydrochloric acid and a 3 cc. ampule of "Lederle's liver extract" intramuscularly twice a week. There was a striking response. By the early part of November her hemoglobin was 65% (Newcomer); red cells, 2,650,000; white cells, 5500; with neutrophils 71%. There were still marked changes in the morphology of the red cells with a tendency to macrocytosis.

When next seen, November 24, she was much stronger, could feed and care for herself and button her gown, but could not walk because her legs "wouldn't track." The numbness had receded to the elbows and midthighs. She had no indigestion and only occasional transient spells of diarrhea. The hemoglobin was 70% (Tallqvist) and the red cells, 3,900,000. She was eating a pound of liver 2 to 3 times a week, taking 9 capsules of "Extralin" a day and receiving an ampule of Lederle's extract intramuscularly in the buttocks once a week. Her subsequent blood counts were as follows, the hemoglobin being estimated by the Tallqvist method:

Date.	Hemoglobin, per cent (Tallqvist).	Erythrocytes, (in millions).
Dec. 1, 1933	75	4.65
8	75	5.00
15	80	4.54
22	75	3.90
26	75	4.50
29	80	4.40
Jan. 5, 1934	80	4.63
12	80	4.48
19	80	5.00
26	75	4.48
Feb. 2	70	4.20

On December 8 stained preparations of the blood showed nothing abnormal but slight achromia. A differential count was not made but the distribution of leukocytes seemed normal. Following the slight drop in the count on December 22, she received 2 ampules (6 cc.) of Lederle's extract a week, and 12 capsules of "Extralin" a day until January 12, when the former dose was resumed. During this time there was a slow but steady improvement in strength and her ability to use her extremities. Her tongue was practically normal, she had a good appetite, practically no gross incoördination of the upper extremities and could walk about the room with support. On January 26 she had a slight stomach upset with nausea and subsequently her appetite was poor. She had not made any change in her habits or taken any of the drugs that have been associated with the development of malignant neutropenia.

She awoke on the morning of February 4 quite tired and after her usual breakfast, vomited. Between then and noon she vomited several times. When seen at noon she looked pale and exhausted. Temperature, 102° F.; pulse, 110. Her throat was slightly red but not more than was to be expected from the vomiting. She was given an enema, a hot water bottle and a powder containing codein sulphate, $\frac{1}{4}$ gr., and acetylsalicylic acid, 7 gr., every 4 hours. She had a fair day and a good night. On February 5 she felt fairly well and was not seen. That night she vomited and retched most of the time and was very hot. When seen on the morning of the 6th she was in moderate shock and complained of a very sore throat. Her temperature was 99° F., pulse, 144 and respirations, 26. Her whole throat was bright red and covered with discrete patches of dry, gray white, tenacious exudate. There was practically no cervical adenopathy. The remainder of examination was negative except for marked dehydration. She was removed to the hospital where her blood showed hemoglobin, 65% (Dare); red cells, 2,830,000; white cells, 500, with 2% neutrophils and no visible platelets. The red cells themselves were remarkably normal. Swabs from her throat showed a few heterogeneous bacilli and cocci, no Vincent's organisms, only a few epithelial cells and no pus cells. Two cultures showed no diphtheria. She was given 10 cc. of pentose nucleotide and 6 cc. of Lederle liver extract intramuscularly, 1000 cc. of 10% glucose subcutaneously and normal saline per rectum. She was very weak and could retain nothing by mouth. Her temperature rose to 104° F., where it remained almost constantly. Her throat and neck remained much the same and except for moderate abdominal distention there were no other physical findings. The glucose was repeated every 8 hours and the nucleotide and liver extract every 6 hours. Blood transfusion was refused. On the night of February 6, blood examination showed hemoglobin, 60% (Dare); red cells, 2,800,000; white cells, 600, with no granulocytes. On the morning of the 7th the hemoglobin was 62%; red cells, 2,910,000; white cells, 500, with no granulocytes. In neither of the last two examinations could granular cells of any type be found on any of numerous slides. She gradually failed and despite stimulation with caffein, died on the morning of February 8.

Partial autopsy (Dr. T. D. Masters) 8 hours after embalming. "A fairly well developed and nourished woman weighing about 95 pounds and appearing about 62 years old. A midline incision was made and the lower half of the sternum and portions of the fourth and fifth ribs on the right side were removed. The gross appearance of these marrows was normal. Additional observations were made through this incision. The pericardium was smooth and glistening and contained about 30 cc. clear fluid. The heart was grossly normal. The various cavities and leaflets were normal to palpation. A portion of the myocardium was removed. The lungs were collapsed. The pleuræ were smooth and glistening. There was no fluid in the pleural cavity. The lungs were crepitant and air-containing everywhere. The liver was the usual size and shape. Its capsule was smooth and shiny. Its surface was yellow-green and firm and the edges were sharp. Because of the restrictions of the permit, no further examination was made."

Histologic examination (Dr. William Bloom, University of Chicago). "The sections of the lung and heart show nothing unusual. The liver tissue although badly preserved shows very prominent phagocytes attached to the walls of the sinuses, but without any evidence of increased phagocytosis such as occurs in some livers from pernicious anemia patients. No blood cell formation could be found and the blood cells circulating in the sinuses are exclusively erythrocytes and non-granular leukocytes; some of the latter, however, are quite large and suggested stem cells. The marrow from the ribs and sternum is exceedingly interesting. Erythropoiesis is proceeding in full blast. Many of the normoblasts have highly constricted polymorphous nuclei. Not a single granular leukocyte or myelocyte was found. The megakaryocytes are quite prominent and perhaps slightly more numerous than usual. Scattered through the parenchyma are more than a few plasma cells, frequently in groups. The stem cells are quite prominent with their basophil cytoplasm and prominent large nucleoli. One could not make a diagnosis of pernicious anemia from the sections in this case but the agranulocytic feature is quite prominent. Most of the marrows of agranulocytic angina have eosinophil myelocytes, but this marrow contained no myelocytes of any type."

Comment. Similar cases have doubtless occurred but are evidently rare, as I have been unable to find any record of them in the literature. Strumia[1] has reported the very interesting relationship between agranulocytosis and acute leukemia. There was no history of exposure to any of the physical or chemical agents or drugs known to produce neutropenia, nor of any previous infection which might have had a bearing on the disease. The examination of the bone marrow showed clearly that the primary defect was in the maturation of the myeloid series into granulocytic forms (Fitz-Hugh and Krumbhaar[2]). It also showed that the pernicious anemia had been adequately treated. Since, at the present time, we know of no substance which will produce or promote maturation of granulocytes there is no reason to suppose that any type of treatment would have availed in this particular case. Certainly such a case might shake one's faith in the possible efficacy of the treatment of a developed neutropenia by liver or liver extract.

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2. Fitz-Hugh, T., Jr., and Krumbhaar, E. B.: Myeloid Cell Hyperplasia of the Bone Marrow in Agranulocytic Angina, Am. J. Med. Sci., **183**, 104, 1932.

BOOK REVIEWS AND NOTICES

A MANUAL OF BIOCHEMISTRY. By J. F. MCCLENDON, Professor of Physiological Chemistry, University of Minnesota Medical School. Pp. 381; 58 illustrations. New York: John Wiley & Sons, Inc., 1934. Price, $5.00.

A CONDENSATION and revision of mimeographed material, this book presents unusual material in a somewhat novel manner. Of its six parts, the first, presents physico-chemical aspects of biology; the second, inorganic compounds; the third and largest section, organic compounds with biologic connections; the fourth, a short summary of the physiology of foods and metabolism; the fifth, about 50 pages of practical laboratory work; the sixth, a table of physical and physiologic properties of 1000 substances with biological connections. The individual reader must decide as to whether he likes his biochemical pabulum in such form. The illustrations cover a wide range, none too well. Presumably done in this fashion for the sake of economy, some might better have been omitted. Though hardly sufficient as a sole support to the neophyte, this book should be a valuable aid to many types of students. E. K.

THE PATIENT AND THE WEATHER. By WILLIAM F. PETERSEN, M.D. With the assistance of Margaret E. Milliken, S. M. Volume II. Autonomic Dysintegration. Pp. 530, lithographed; 249 illustrations. Ann Arbor, Mich.: Edwards Brothers, Inc., 1934. Price, $6.50.

THE waggish comment by Mark Twain that "everybody talks about the weather but nobody does anything about it," is being refuted by this series of five or six volumes. The present belated one, follows Volume III and, seemingly, precedes Volume I. It concerns itself with headache, epilepsy, eclampsia and premature delivery, mucous colitis and gastric ulcer, the neuroses, urticaria, asthma, arthritis, glaucoma, ear, teeth, hair and therapeutic implications.

In general, the persons considered are those unusually responsive to their environment and termed by von Bergmann as "vegetatively stigmatized." Effects occur through changes in temperature, atmospheric pressure, vapor pressure and air ionization, bringing about either vascular spasm or relaxation, thereby affecting the blood supply to the tissues. Considering an acute infection such as appendicitis, it is stated: "actually the bacteria invade the organ after an anoxemic injury to the tissues. The sequence is not first bacterial penetration, then inflammation! On the contrary it is first tissue dysfunction—then invasion— and the combination of the two results in inflammation."

Many graphs are included and their comprehensiveness may be illustrated by one from a subject with arthritis, showing the metrograph, the clinical and subjective record and in addition the following curves for a 24-day period: Basal Metabolic Rate; Leukocyte Count; Methylene Blue Reaction Time; Respiratory Rate; Morning Temperature; Systolic and Diastolic Blood Pressure; Pulse Rate; Cholesterol; Phosphates; CO_2 Content; Blood pH; K/Ca Ratio; Potassium; Calcium; Serum Protein; Capillary Permeability; Blister Time. There is an abundant bibliography but no index. N. Y.

DISEASES OF THE RECTUM AND COLON AND THEIR SURGICAL TREATMENT. By J. P. LOCKHART-MUMMERY, F.R.C.S. (ENG.), M.A., M.B., B.C. (CANTAB.), Senior Surgeon to St. Mark's Hospital for Cancer, Fistula, and Other Diseases of the Rectum, etc. Pp. 605; 250 illustrations. Second Edition. Baltimore: William Wood & Co., 1934. Price, $10.00.

IN the eleven years that have elapsed since this book first appeared, the advances in diagnosis and treatment have been so numerous that an extensive revision was obviously in order. This the distinguished author seems to have satisfactorily accomplished, and many will pardon to one of his position a dogmatism which at any rate conduces to clarity. The new chapter on precancerous conditions is a timely warning of the tendency of many benign neoplasms to become malignant. E. K.

THE NERVOUS PATIENT. A Frontier of Internal Medicine. BY CHARLES PHILLIPS EMERSON, M.D., Research Professor of Medicine, Indiana University, Indianapolis. Pp. 453, Philadelphia: J. B. Lippincott Company, 1935. Price, $4.00.

THE scope of this book is much more inclusive than its title would indicate. The author makes clear in his introduction that he has an individual approach to the "Nervous" patient, including in this category serious organic diseases, personality problems, disturbances of the internal secretions, psychoneuroses and mild insanity. He says, "to understand the 'nervous' patients, therefore, we must study not only purely functional conditions, but also the early stages of practically every physical and mental disease." Accordingly the author has presented 30 chapters in which he has included psychopathology, blood chemistry, allergy, the autonomic nervous system, organs, as the eye and ear, systems, as the respiratory and the gastro-intestinal, with certain organic and "nervous" manifestations found in each, the diseases encountered in neurology and psychiatry, including the psychoneuroses, disorders of sleep, disturbances within the sex life and suggested treatments for all.

Obviously, such an encyclopedia of medicine in 453 pages by one author is an ambitious project, and as such is likely to have deficiencies. He feels that the approach to the problem from the angle of psychopathology and by the psychiatrist is not the solution to the problem of the "nervous" patient. He says, "their field and ours overlap but little. Ours, none can enter save the internist trained in the accurate diagnosis of that great variety of organ dysfunctions which physical disease produces. He alone can evaluate those elements which the patient's disturbed personality injects into the clinical picture of organic disease; he alone can recognize those almost exact imitations of these same organic diseases which have their origin in the emotional life of the patient."

Yet, the author admits being untrained in the field of psychiatry. The inference, then, is that either he has peculiar acumen for discerning the interrelations of emotion and body functions, or the psychiatrist has spent his years of training for naught. Psychiatrists will often fail to agree with the author's optimistic concepts of certain entities such as Neurasthenia which he would define "as a well unified anxiety condition, developing as an incident in the previously efficient life of a person otherwise not psychoneurotic, based on some clearly recognized unwelcomed state, physical, social, economic, etc., all the psychic elements of which either are clearly in consciousness or easily can be brought there, and which, once relieved, shows no tendency to recur."

He invokes the various schools of psychopathology in understanding the

neurotic but largely rejects their views in treatment. Such severe neuroses as psychasthenia he would treat by, rest, routine, regular schedule, diet, Emerson's Essays, committment of the Psalms to memory and the recital of one daily to his physician. He admits that some psychasthenias have been helped by psychoanalysis but that these must have been cases in which the patient merely accepted his disabilities.

There are some valuable suggestions in the understanding and management of the "nervous" patient, and occasional short case references. But the author's ambivalent attitude to psychopathology is unfortunate. He is repeatedly accepting, then rejecting its value etiologically in a manner that would be very confusing to the uninitiated reader who wished to get information for the understanding and management of the neurotic patient.

The author says that his book is intended for the general practitioner. It is written in a very interesting readable style, and for a survey of the author's own approach to medical problems it is well worth while. But it is not recommended for the reader who might infer from its title and the author's preface that it contained the most recent advances concerning the mental and physical disorders of psychogenic nature. O. E.

KORONARINFARKT UND KORONARINSUFFIZIENZ. In Vergleichender Elektrokardiographischer und Morphologischer Untersuchung. By Professor Dr. MED. FRANZ BÜCHNER, Vorstand des Pathologischen Instituts am Horst-Wessel Krankenhaus der Stadt, Berlin; Professor DR. MED. ARTHUR WEBER, Vorstand des Balneologischen Universitätinstituts in Bad Nauheim, DR. MED. BERTHOLD HAAGER, Assistent am Balneologischen Universitätsinstitut in Bad Nauheim. Pp. 104; 116 illustrations. Leipzig: Georg Thieme, 1935. Price, Rm. 15.

ELECTROCARDIOGRAPHY seems now to have reached a development that requires specialized presentation. Only one field is covered in this book, the comparison of electrocardiographic and morphologic changes in coronary disease. Produced from the Horst Wessel Hospital with the aid of the Notgemeinschaft der Deutschen Wissenschaft, this work in its introduction shows a refreshing acquaintance with the contributions from other countries and a willingness to accord them proper significance. It is regrettable, however, that more experimental findings, the recent work on the Thebesian System and Leary's two types of coronary disease were not included, even in this short space.

Two-thirds of the book is made up of the data on 43 cases (protocols on the left, electrocardiograms, photographs of the heart, and diagrams of the lesions on the right). This constitutes evidence of permanent value. The labor required from the reader in making interpretations will be amply repaid him. E. K.

ECONOMIC PROBLEMS OF MEDICINE. By A. C. CHRISTIE, M.S., M.D., Professor of Clinical Radiology, Georgetown University Medical School, etc. Pp. 242. New York: The Macmillan Company, 1935. Price, $2.00.

THIS little volume is from the pen of a practising physician who was a signer of the minority report of the Committee on Costs of Medical Care. Early chapters concerned with the economic aspects of Medical Education, private and hospital practice including the training of specialists, the relation of the physician to medical organizations and the community are all reflections of the viewpoint of the average intelligent physician. They may well be considered as supplementing discussions of these subjects in "Medi-

cal Care for the American People," a work which reflects the attitude of professional sociologists.

The author also presents an analysis of medical care under Workmen's Compensation laws, contract practice and the various forms of Health Insurance in vogue in Europe. His views on these subjects differ from those of the extreme liberal and the sociologist but are set forth without emotional display, for which he is to be congratulated. He further supplements the much discussed "Medical Care for the American People" by describing modest attempts which have been started in a number of communities as local solutions to the vexing problems of providing adequate care to all people at a reasonable price and with due regard for community responsibility for its indigent. The author's suggestions and requirements for a comprehensive plan for medical care will probably not please the ultra conservative physician who wishes nothing changed and will certainly not satisfy the professional sociologists who wish to change everything and who seem unwilling to await an orderly evolution. It will appeal to the thoughtful person, whether layman or physician, who prefers moderation in a discussion of what is undoubtedly the most important medical problem of our generation.

E. T., JR.

MANUAL OF DIABETES. By J. J. CONYBEARE, M.C., M.D., OXON., F.R.C.P., Physician to Guy's Hospital. Pp. 123. New York: Oxford University Press, 1935. Price, $2.00.

THE need for a thorough knowledge of the practical details of diabetic treatment on the part of the patient as well as the physician receives full consideration in this book. In fact, information of this kind has been summarized in a lengthy appendix which, as the preface tells us, is sold separately at low cost. The main text is on the whole successful in its aim "to outline in concise form the general considerations which govern the physician's treatment of diabetes," though many a physician will be disappointed in not finding fuller treatment of some detail on which he wants more information.

E. K.

NEW BOOKS.

The Doctor's Bill. By HUGH CABOT. With an Introduction by A. LAWRENCE LOWELL. Pp. 313. New York: Columbia University Press, 1935. Price, $3.00.

Geschichte der Physiologischen Chemie. By DR. FRITZ LIEBEN, Privatdozent an der Universität, Wien. Pp. 741. Wien: Franz Deuticke, 1935. Price, M. 20.

Some Notable Epidemics. By H. HAROLD SCOTT, M.D., F.R.C.P. (LOND.), D.P.H., D.T.M. and H. (CAMB.), F.R.S.E., Assistant Director, Bureau of Hygiene and Tropical Diseases. With a Preface by W. W. JAMESON, M.A., M.D., F.R.C.P., Barrister-at-Law, Professor of Public Health in the University of London; Dean of the London School of Hygiene and Tropical Medicine. Pp. 272. Baltimore: William Wood & Co., 1934. Price, $4.75.

Medizinische-chemische Bestimmungsmethoden. Eine Anleitung für Studierende der Medizin und für Laboranten. By KARL HINSBERG, Vorsteher der Chemischen Abteilung des Pathologischen Instituts der Charité, Berlin; Privatdozent an der Universität Berlin. Volume 1. Darstellung der allgemein gebräuchlichen und der wichtigsten quantitativen Methoden. Pp. 93; 29 illustrations. Berlin: Julius Springer, 1935. Price, Rm. 4.80.

The Cosmic Way to True Civilization Through Parenthood. By GEORGE H. DONAHUE. Pp. 68, n.p., 1934. (No price given.)

Syphilis. Ihr biologischer Ursprung und der Weg zu ihrer Ausrottung. By DR. MED. FERDINAND THUGUT. Pp. 109. Stuttgart: Ferdinand Enke, 1931. Price, Rm. 4.00.

Clinical Management of Syphilis. By ALVIN RUSSELL HARNES, M.D., Chief of Congenital Luetic Clinic, New York Hospital. Pp. 71; illustrated. New York: The Macmillan Company, 1935. Price, $1.50.

Fifty Years a Surgeon. By ROBERT T. MORRIS, M.D. Pp. 347. New York: E. P. Dutton & Co., Inc., 1935. Price, $3.50.

Manual of Diabetes. By J. J. CONYBEARE, M.C., M.D. (OXON.), F.R.C.P., Physician to Guy's Hospital. Pp. 123. New York: Oxford University Press, 1935. Price, $2.00. (Review, p. 119.)

Emotions and Bodily Changes. A Survey of Literature on Psychosomatic Interrelationships, 1910–1933. By H. FLANDERS DUNBAR, M.D., PH.D., Departments of Medicine and Psychiatry, Columbia University. Pp. 595. New York: Columbia University Press, 1935. Price, $5.00.

NEW EDITIONS.

Electrotherapy and Light Therapy. By RICHARD KOVÁCS, M.D., Clinical Professor and Director of Physical Therapy, Polyclinic Medical School and Hospital, New York; Physician in Charge Physical Therapy, City Hospital, New York, etc. Pp. 696; 263 illustrations and 1 colored plate. Second edition, thoroughly revised. Philadelphia: Lea & Febiger, 1935. Price, $7.50.

This successful attempt to show the practitioner the possibilities and limitations of physical therapy deserves its reputation as the best book on the subject in English. This edition adds a new chapter on the physiologic effects of electricity, together with new material on iontophoresis, the physics and use of thermionic tubes, diathermic hyperpyrexia and so on. Electrosurgery and light therapy have demanded especial additions.

The Biochemistry of Medicine. By A. T. CAMERON, M.A., D.Sc., F.I.C., F.R.S.C., Professor of Biochemistry, Faculty of Medicine, University of Manitoba; Biochemist, Winnipeg General Hospital; and C. R. GILMOUR, M.D., C.M., F.R.C.P. (C.), Professor of Medicine and Clinical Medicine, University of Manitoba; Physician, Winnipeg General Hospital. Pp. 518; 31 illustrations, 17 tables. Second edition. Baltimore: William Wood & Co., 1935. Price, $6.00.

"This book is designed both for the student of medicine receiving clinical instruction in the later years of his course, and for the physician who received no special instruction in the medical applications of biochemistry. In this new edition the chapter on the endocrine secretions has been largely rewritten, and a brief account is included of the important discovery of anti-endocrine compounds . . . . New subjects dealt with briefly include von Gierke's glycogen disease, the diseases concerned with incorrect lipoid storage, tyrosinosis, the dinitrophenol treatment of obesity, the glycin treatment of myasthenia gravis, and the pentose-nucleotid treatment of agranulocytosis." The summary at the end of each chapter is a valuable feature, if properly used.

Handbook of Anesthetics. By J. STUART ROSS, M.B., CH.B., F.R.C.S.E., Late Lecturer in Practical Anæsthetics, University of Edinburgh, and H. P. FAIRLIE, M.D., Anæsthetist to the Western Infirmary, The Royal Hospital for Sick Children and the Dental Hospital, Glasgow. With a chapter upon Local Anæsthesia by W. QUARRY WOOD, M.D., F.R.C.S.E., Assistant Surgeon, Edinburgh Royal Infirmary. Pp. 299; 66 illustrations. Fourth edition. Baltimore: William Wood & Co., 1935. Price, $4.00.

Dr. Fairlie, whose name first appeared on this book in the previous edition, now assumes sole responsibility; emphasis, however, continues to be laid upon first principles. New methods and new apparatus have been conservatively added; ether (including 2 lines on divinyl ether) occupies but 30 pages and chloroform a paltry 17. The chapter on the choice of anesthetic is valuable and could well have been further extended.

PROGRESS
OF
MEDICAL SCIENCE

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RECENT ADVANCES IN PERIPHERAL VASCULAR DISEASE.

In recent years investigation in peripheral vascular disease has grown rapidly. The increasing attention to these disorders is reflected in the remarkable growth of the number of clinics established for their study. This shift in interest from the central to the peripheral vascular system has led to the development of a tremendous literature upon the subject.

Etiology. *Arteriosclerosis.* The work of Popoff[1] on the digital vascular system points directly to changes of etiologic importance in the peripheral arteriovenous anastomoses in diabetic and arteriosclerotic gangrene. The arteriovenous anastomoses, which he terms the glomic system, are described in detail, with their local and general functions. Comparative studies of the glomic system in arteriosclerotic and diabetic gangrene show that both depend upon a sclerotic process and contrary to present views the two processes are not identical. In arteriosclerotic gangrene the changes are due primarily to hyalin degeneration in the afferent artery of the glomus, whereas in "diabetic gangrene the intima of the Sucquet-Hoyer canal (the arteriovenous anastomosis proper) and that of the preglomic arterioles are the first to show signs of primary degenerative changes, while the intima of the afferent artery of the glomus remains intact. These changes bring about an understanding of the trophic and vascular changes observed in the digits."

The dissections of Wollard and Weddell[2] in patients with diabetic and arteriosclerotic gangrene also demonstrated distinct differences in these two processes. They injected the arteries of amputated legs and made arteriolar counts at various levels in the foot. In senile gangrene no transformation or new formation of arterioles occurred, but in diabetic gangrene there was a tendency for the arterioles to increase in both these ways. In senile gangrene the finer vessels actually tended to disappear. In thrombo-angiitis obliterans the tendency for these vessels to increase was at a maximum.

Raynaud's disease is described as a localized form of vasoconstrictor disturbance characterized by clinical phenomena dependent upon excessive constriction of small vessels. Lewis and Pickering[3] have recently published evidence to show that the term Raynaud's disease has not

been suitably defined, and that it probably cannot be defined to common agreement. These authors feel that there may be several or many quite distinct maladies grouped under the term. That this is undoubtedly true in general usage was shown by Allen and Brown[4] in an excellent review applying the criteria of Raynaud to published cases. Observations of Raynaud's own case reports showed a lack of correlation with his criteria in some instances.

Lewis and Pickering use the term "Raynaud's phenomenon" to describe closure of arteries of the size of the digitals with resulting discoloration of the part. Closure may occur with or without local nutritional changes. While cooling of an artery causes narrowing due to vasomotor constriction and direct response of the vessels, experimentation showed that vasomotor constriction alone was not sufficient to close the digital artery. Closure was ascribed to a local fault, the nature of which is still obscure. This concept ascribes the phenomenon of Raynaud's disease to the bloodvessel itself and not to the nervous system. The fact that cooling would not produce changes when the vasomotor nerves were sectioned was attributed to insufficient cooling, without vasomotor tone.

Sixteen of 33 cases of intermittent spasm of the digital arteries (dead finger, for example) gave a family history which lead Lewis to believe that this phenomenon may often be an inherited peculiarity. The fact that some cases with scleroderma showed skin hardening preceding the attacks cast doubt upon the skin changes always being secondary to the vasospastic changes, and justified another group. Cases developing after injury, vibration, working on air pressure drills and so on, he believed constitute another yet obscure group. He did not ascribe those cases with bilateral massive gangrene of the ends of the fingers to continuous spasm of the arteries. "The attack is too prolonged and areas involved too sharply defined and unvarying, and the vessels could not be opened by warmth or other means as with all undoubted cases of spasm. Evidence of obstruction in the digital vessels has been shown in these cases and there is no evidence to support the idea that the thrombosis could result from the spasm." Reactive hyperemia would prevent it also. Furthermore, spasm is known to occur in association with other types of organic obliterative disease. The authors point to the problem of spasm as a determining factor in intimal or thrombotic changes with resulting obstruction in small arteries, as a subject for future study.

Thrombo-angiitis Obliterans. The etiology of thrombo-angiitis obliterans remains unknown. Although most workers hold one of two main theories, other theoretical explanations have been brought forward as possibilities. The diversity of opinion itself is the best evidence of the ignorance of the cause of thrombo-angiitis obliterans. The infectious theory with toxin formation and spread, based chiefly on transplantation experiments, has found no bacterial support. In Popoff's[1] study of the arteriovenous anastomosis of the digit in thrombo-angiitis obliterans he found no support for inflammation or thrombosis of the vessels as a causative agent. He states that the glomic system (the normal arteriovenous anastomosis in the digit) appeared to be free from primary specific changes and describes a "hitherto unknown vascular anomaly of the peripheral digital system" as a cause of the trophic

and inflammatory changes. This abnormality is the presence of an anastomosis between the arteries and veins, differing from the usual type in size, structure and topographic distribution. In his normal and pathologic material covering 840 individual blocks studied by serial sections, he found these abnormal anastomoses only in cases of thrombo-angiitis obliterans. He suggests that "comparative results of studies on the digital glomus demonstrate that neurovascular and trophic changes observed in the digits in many instances may be due primarily to local changes in the glomus and not to inflammatory degeneration or obstructive changes in the large arteries and veins of the extremity. In looking over descriptions of symptomatology in thrombo-angiitis obliterans it is significant that local chronic cyanosis of the toes may precede gangrene of the foot by months and even years and may be the only objective sign. Postural color changes in the earliest stages occur only in the tips of toes."

Confirmation of Popoff's work would modify completely the conception of thrombo-angiitis obliterans.

The use of tobacco as a cause of thrombo-angiitis obliterans has been a subject of much study. The reviewer finds no reports that increased smoking among women has increased the percentage of cases found in women. The report by Maddock and Coller[5] of diminished skin temperature following smoking of cigarettes, recently confirmed by Johnson and Short,[6] added impetus to this theory. The allergists, too, have continued attempts to correlate allergy, tobacco and thrombo-angiitis obliterans. Sulzberger[7] found that 78% of 79 patients with thrombo-angiitis obliterans had immediately positive skin reactions to tobacco extracts, but also did 36% of smokers without thrombo-angiitis obliterans and 16% of the non-smokers tested. Prausnitz-Küstner antibodies were found in only 1 case. Sulzberger states that, as the positive tests in patients with thrombo-angiitis obliterans correlated with clinical evidence incriminating tobacco, his results were highly suggestive that sensitization of the vascular system to tobacco may play at least a contributory rôle in many cases. Harkavy and Romanoff[8] conclude that the strikingly larger number of positive skin tests to tobacco in thrombo-angiitis obliterans (69%), compared to 11% in controls, indicate that tobacco is the dominating reacting allergen in thrombo-angiitis obliterans. Chobot,[9] however, found many reactions in allergic children who never smoked, one being in a child of 3. Of 53 asthmatic children from 3 to 12 years of age, only 6 (11%) were negative. The results were presented to emphasize caution in interpretation of the diagnostic tests. Their significance is not known, but Chobot believes it is analogous to what is seen when patients are tested with solutions of morphin and histamin.

To demonstrate the diversity of opinion in the etiology of thrombo-angiitis obliterans, although published 4 years ago, one may mention the work of Kaunitz[10] on chronic ergot poisoning. A study of the literature of epidemic ergotism convinced Kaunitz that the cause of some vasomotor and trophic disease could be traced to endemic ergotism. Obviously this theory has not been proved. All the evidence is indirect. It has long been known that males are more susceptible to ergot poisoning than females and that ergotism produces gangrene in young and middle aged males but rarely in females. It has also been shown that

the rye fields of this country are often contaminated, and that grains from some fields are infected so heavily "that every head may have one or more sclerotia." Kaunitz also quotes Morgan in a description of an epidemic of ergot poisoning in England in 1928. Symptoms occurred only in Jews who ate rye bread. These data, while interesting, are not convincing, and are offered in this light only.

In a report of 2 cases of thrombo-angiitis obliterans occurring in women, Silbert[11] again reviews the possibility of the dependence of thrombo-angiitis obliterans upon a constitutional hereditary factor. Evidence of horizontal and vertical inheritance is very meager in reported cases, but the great preponderance of cases in males and in the Hebrew race surely suggests such a sex-linked constitutional factor.

Sporadic efforts to associate etiologically thrombo-angiitis obliterans and thrombophlebitis migrans have been made, but usually the latter has been considered a separate disease. Many cases have been reported without any apparent arterial disease. However, phlebitis as a manifestation of thrombo-angiitis obliterans is well known. d'Abreu[12] in England reported a case, clinically thrombophlebitis migrans for 40 years, which developed arterial symptoms and at postmortem proved to be one of thrombo-angiitis obliterans.

Periarteritis Nodosa. The view that periarteritis nodosa is a manifestation of syphilis has long been discarded. The course and nature of the disease suggests infection as a cause and a gamut of such causes has been offered. The filterable virus theory has many adherents, but the work of Friedberg and Gross[13] in which 4 of 8 cases autopsied presented conclusive evidence of rheumatic heart disease appears significant. Attention to a possible relationship between periarteritis nodosa and rheumatic fever has been made before. However, the rigid criteria of the presence of Aschoff bodies in the myocardium and other manifestations of rheumatic fever, associated with the typical findings of periarteritis nodosa have not been used. Arterial lesions usually described in rheumatic fever have other characteristics.

Erythromelalgia. Lewis[14] has abandoned the term erythromelalgia. He believes that a number of diseases, including cases of thrombo-angiitis obliterans and other arterial diseases, have been placed in this diagnostic pigeon-hole because of the symptom of burning pain. This type of pain describes a "susceptible state" of the skin. This is a local affair, produced by friction, warmth, and dependency of the part, which, when combined with redness on dependency, usually leads to the diagnosis of erythromelalgia. Lewis and Hess[15] have previously shown that a skin injured in any way may enter this susceptible state, became hyperalgesic, with the threshold of heat lowered, and when the temperature passes 32° to 34° C. develop burning pain.

The final criterion for the diagnosis of erythromelalgia has been a vasodilatation, generally considered of vasomotor origin, which often produces a venous pulsation and an objective increase in the temperature of the part. Color may deepen without active dilatation, so that color change alone does not signify active hyperemia. Lewis found there was very little in reported cases to indicate that the temperature of the part was greater than one would expect in any limb under similar circumstances, and no objective evidence appeared to support the presence of abnormal vasodilatation. There is, therefore, no evidence

that abnormal vasodilatation based on vasomotor phenomenon must occur. The skin is in the abnormal condition, Lewis states, and when an increased blood flow raises the temperature to the proper level, burning pain results. There is no evidence that abnormal dilatation is necessary. Lewis believes that the term "erythromelalgia" should be discarded as a term to designate a disease and that some other term such as "erythralgia" should be employed to designate the painful redness of the skin.

Diagnosis. *Subjective Findings.* Goldsmith and Brown[16] have offered a tentative classification of the pain in thrombo-angiitis obliterans which is helpful in the diagnosis of the immediate cause of the pain, and consequently helpful in the institution of treatment against the offending etiologic agent. The classification is based upon an analysis of 100 cases. Pain is divided into two major groups: (1) pain on exercise, and (2) pain at rest. Pain dependent upon exercise may arise from phlebitis or intermittent claudication, the characteristics of which are well known. Rest pain is of several distinct types. So-called pretrophic pain may be well localized in the feet and hands, is burning in character, worse at night, and aggravated on dependency. This type appears to correspond to the erythralgia of Lewis.[14] The term pretrophic is used because ulcers and gangrene are prone to develop at the site of pain. Trophic pain, that of ulcer and gangrene, develops gradually, is often severe, is stinging and burning in character, and is accompanied by hyperesthesia of the part. The characteristics of the pain of inflammation vary with the location. Arteritis sometimes leads to an aching, generalized pain with, of course, coldness of the part, while phlebitis leads to a more localized form with tenderness over the veins and exacerbations on exercise. Acute occlusion with massive ischemia causes a sudden tenderness at the site of occlusion with severe generalized pain radiating peripherally. The last classified type, ischemic neuritis, is very severe, diffuse, and extends over large areas not always corresponding to the distribution of the nerves. It is a paroxysmal, tearing pain, which may radiate from one end of the extremity to the other. Skin discoloration may be associated. Exacerbations may last several hours and the pain itself may be present irregularly for 1 to 8 months. Neurologic studies in these cases may show changes in reflexes and sensory nerves.

Physical Examination. Great stress has been laid upon the palpatory findings in the differential diagnosis of vasospastic and organic occlusive disease. The importance of establishing definitely the normal variations in palpatory findings in the absence of disease, as a groundwork for interpretation of the abnormal, has led Reich[17] to study the arterial network in the lower extremities in 500 healthy individuals. He found an absence of the dorsalis pedis pulse in 4%, absence of the posterior tibial in 5%, and in 8% the dorsalis pedis was found in a location outside the usual position. The study was continued with a dissection of the arterial system of the lower extremity in 70 legs of 35 white cadavers. It was found that the vessels below the knee presented many variations from the usual picture found in textbooks of anatomy. Fifty-two (74%) of the limbs had predominant dorsalis pedis arteries; in 5 (7%) the lateral tarsal artery was the larger and in 10 (14%) the lateral tarsal was the main artery of the dorsum of the foot. In 7 cases the dorsalis

pedis was very small and in 3 was entirely absent. The author offers as an explanation for these unusual variations the phylogenetic development of the human, and states that "it is plainly due to the relative recent transformation in vascular pattern of the human leg and foot that the arterial channels of the dorsum present so variable a character." The posterior tibial arteries in the same study were absent in 4 legs (6%) and in 2 (3%) were very small. The phylogenetic explanation is extended to these vessels as well. Both tibials and the peroneal are described as of recent origin, and in man alone of all primates it is stated we find the complete pattern of new connections between the popliteal and the arterial supply of the dorsum and sole of the foot.

It is probably true, then, from Reich's statistics that in 100 extremities with no occlusive peripheral vascular disease the usual palpation in the anatomic location of the dorsalis pedis would disclose a pulsating artery in approximately 80. In 14 of these trials it would be necessary to palpate more laterally in the region of the head of the third metatarsal bone. In about 4 of the legs the possibilities of feeling a pulsation in both regions would exist, but with small arteries this might be difficult to determine. In a like number no pulsation at all would be found. For the posterior tibial, approximately 3 of 100 limbs would show a very weak pulsation and 3 to 5 no pulsation at all.

Certain other factors as well may make palpation of the arteries difficult. Edema, adiposity, and ligamentous attachments, especially in the case of the posterior tibial, sometimes add to the diagnostic handicaps. One must agree from this work that, although palpation of the arteries of the foot is a most important diagnostic procedure, the absence of a pulsating artery is not pathognomonic of disease and other evidence must be on hand for diagnosis, especially in doubtful cases.

That thrombo-angiitis obliterans is not exclusively a disease of the extremities, and may add to diagnostic difficulties elsewhere, finds further support in 2 recent reports.[18,19] Averbuck and Silbert, in a study of the causes of death in thrombo-angiitis obliterans have shown that coronary, mesenteric and cerebral thrombosis are not uncommon, and that their occurrence in thrombo-angiitis obliterans is not merely coincidental. Of 47 cases 22 died of vascular accidents.

Roentgenography. Search for objective findings to confirm a diagnosis of peripheral vascular disease often leads to attempts to demonstrate calcium in the arterial wall roentgenologically. The clinical significance of such findings in occlusive disease, however, has not been satisfactorily established. One finds sporadic reports of occasional cases[20] in which the more marked calcification occurred in the opposite or non-symptomatic side. Lansbury and Brown[21] have intestigated this problem recently to clarify the questions of the clinical importance of calcification, the possible correlation between calcification and clinical arterial occlusion, and the possibility of determination of the nature of the occlusive process by the presence or degree of calcification. Studies were carried out on a group of clinically negative controls from 50 to 80 years of age, a group with arteriosclerosis obliterans, and a group with thrombo-angiitis obliterans. Results were interesting and enlightening. In arteriosclerosis obliterans the findings closely paralleled the control series with the curve of incidence of calcification in the various age

groups quite similar, but slightly higher in occluded cases. Calcification in the age period from 65 to 70 years was greatest in both groups. Results indicated that calcification after the fifth decade was probably a normal process and consequently occlusion may or may not be superimposed upon it. In grading the degree of calcification it was found that no significant correlation could be obtained between the degree of calcification and the presence of occlusion, except when calcification was entirely absent, when the chances of the arteries being open or closed were 70% to 30%.

In thrombo-angiitis obliterans calcification was less frequent than in either of the other groups for similar age periods. In this disease for example, at 54 years of age, calcification occurred in 14% of the patients, in the controls in 40 to 50%, and in arteriosclerosis obliterans in a somewhat higher percentage. In differentiating the latter disease from thrombo-angiitis obliterans one might say, then, that calcification as shown roentgenologically may be of some value. However, demonstration of calcification does not give objective evidence favoring the presence or absence of occlusion and one must guard against erroneous conclusions from its presence. In the opinion of Lansbury and Brown degenerative changes, intimal thickening, and medial calcification can diminish the lumen of arteries but do not progress to a stage of complete occlusion in the larger arteries, and calcification alone without an occluding thrombosis is not clinically significant.

Postmortem observation of the arterial lumen may lead to false conclusions in arterial patency. Stewart, Birchwood and Wells[22] emphasize that in dissecting the coronary arteries one often notes that plaques appear to impinge markedly upon the arterial lumen but that when these arteries are placed under a tension comparable to that of the systemic blood pressure the apparent narrowing may disappear and the integrity of the blood column be maintained. Roentgenographic confirmation of these changes were obtained by injection of the coronary circulation of excised hearts with radio-opaque media.

Clinical arteriography, the use of radio-opaque media by intra-arterial injections into the living human, is gaining ground as a diagnostic procedure.[23–27] Allen and Camp[26] have considered its diagnostic value and evaluated the method in reference to the entire group of peripheral vascular cases. They have found that approximately 85% of such cases can be correctly diagnosed by a good history and thorough physical examination. Increases in this percentage depend upon special methods of study, capillary microscopy, oscillometry, skin temperature studies, color changes to posture and the other special tests. After use of these procedures a small number of cases remain in which arteriography is the most important diagnostic aid. While most cases do not require the procedure, it is extremely important in those few not diagnosable otherwise. This is exemplified in thrombo-angiitis obliterans when the obliteration is in the small digital arteries. The method demonstrates the extent and location of collateral circulation, the location and extent of the disease, and the nature of the pathology, not only for diagnosis but as a guide to prognosis and treatment as well.

Vasodilating Procedures. In the past 10 years the methods for determination of spasm of bloodvessels have increased markedly. Not only have these methods made possible differentiation of doubtful

cases of vasospastic and occlusive disease but they have also made possible the determination of the extent of vasospasm present in occlusive disease. In thrombo-angiitis obliterans, for example, spasm may play a dominant or minor rôle in the symptomatology. If important in the symptomatology, operative procedures for relief of spasm are very effective therapeutic weapons, but if spasm is of minor importance these operations give little relief. As a consequence diagnosis of the physiologic state of vasospasm may be more important in instituting therapy than the anatomic diagnosis of thrombo-angiitis obliterans.

A discussion of the well established methods for the estimation of vasospasm does not constitute a part of this review. Procedures in general use depend upon an interruption of the vasoconstrictor nerves between the parts supplied and the central nervous system. The more important methods are local anesthesia, sympathetic ganglion block, spinal anesthesia, artificial fever by typhoid vaccine, or wrapping patient in blankets, heating of the hands or feet, Roentgen ray to the lumbar region, and the use of drugs. The release of spasm is measured indirectly by determinations of skin temperature.

All these methods are not of equal value. The heating of the body or extemities, for example, while relatively simple and without hazard is not as effective as spinal anesthesia or high fever. Pickering and Hess[28] have noted that warming the body of normal subjects produces vasodilatation more easily in the hands than in the feet. This delay occurred when the extremities were exposed to temperatures below that of the body and the onset was delayed in cool hands or feet or in one cold digit. The fine localization of the changes on cooling a part tend to rule out sympathetic action and favor the local action of cold on the vessels as the cause, so that when the body and digits are cool the vessels are constricted both by sympathetic tone and by a direct action on the vessels. It is the direct action which delays the response on cooling. Observations also suggest that warming removes only a part of vasoconstrictor tone from the feet, the remainder being permanent unless the sympathetics are blocked. This change explains the failure of vasodilatation in the feet as compared with the hands. The difference in response of the fingers and toes is important clinically, for with this test an incomplete response cannot be used as indication of the presence of disease.

Shaw[29] believes that the estimation of skin temperature rise is diagnostically useful in vasospasticity of the dermal bloodvessels and is particularly applicable to Raynaud's and other purely spastic conditions. However, in occlusive disease, such as thrombo-angiitis obliterans, he believes it of only slight value because of possible error, because considerable hyperthermia is not necessary for the relief of symptoms or the healing of peripheral lesions, and because, although vasospasticity exists in the surface bloodvessels, ganglionectomy is unable to overcome the effects of a complete block of the deeper vessels.

Miscellaneous Procedures. Recently Bernheim[30] has published a preliminary report on a simple technique for the interpretation of bloodvessel disease of the legs. The patient sits with the legs crossed and the small swing of the foot, which is synchronous with the cardiac cycle, is recorded on a moving drum by a rod fastened to the shoe. Bernheim believes this method reveals accurately the state of the cir-

culation in the leg and not pulsations from any one particular artery such as the popliteal. Until further work is done to establish the efficiency of the method one must withhold opinion as to its possibilities.

Therapy. Advances in therapy in peripheral vascular disease have kept pace with, and to a great extent have depended upon, the improved diagnostic procedures.

General Procedures. Samuels[31] has reported results in thrombo-angiitis obliterans with a method of treatment he had described previously. The routine is marked by extreme conservatism, which he regards as obligatory. In over 300 patients in 8 years he has found only one requiring amputation. This constitutes less than 1% as compared with 14% or more in the work of others. It is the adherence to a general outline of therapy, "an intelligent combination of various fundamental factors," which assures success. Briefly the procedure consists of: (1) bed rest; (2) abstinence from smoking; (3) intravenous saline injections, and (4) local treatment of ulceration and gangrene. Bed rest he believes absolutely essential. The lower extremities must be horizontal. This position controls edema, which even if very localized, retards healing and may be the one factor which causes ulceration to persist. Smoking he considers harmful. Evidence for this is given in the section on etiology above. Samuels cites the clinical course of gangrene as he has seen it in tobacco users as the criterion for withholding tobacco. Intravenous saline injections are used to lower blood viscosity upon the basis of previous work by Mayesima, Koga, Willy Meyer, Silbert and others. An outline of the technique used is given. Local treatment of ulceration and gangrene is carried out by adherence to correct surgical principles, in order to aid in formation of a line of demarcation, to control pain and to maintain asepsis. It is important, he states, to control the pain of gangrene until the acute process subsides to avoid unnecessary amputation. Samuels feels that sympathectomy and ganglionectomy have no place in the treatment of thrombo-angiitis obliterans. He has found no cases of massive gangrene healed by these methods, and the small ulcers or areas of gangrene so treated he believes have healed because of the confinement to bed postoperatively.

Drugs. Theobromin, because of its vasodilating properties centrally, has been used in peripheral vascular disease. Scupham,[20] who used the drug previously with some success in thrombo-angiitis obliterans, has extended his observations to arteriosclerosis with intermittent claudication, Raynaud's disease and allied vasospastic disorders. The latter group showed no improvement, but arteriosclerosis and thrombo-angiitis obliterans with a large element of spasm responded sufficiently well to consider the drug a valuable adjunct in their treatment. Best results were obtained with theobromin-sodioacetate. Newell and Allen,[32] however, found best results with theobromin sodiosalicylate when given intravenously. Results orally were inconstant. Their conclusions were similar to Scupham's in that the drug was described as of little value in treatment of peripheral vascular disease except as an adjunct.

Kovács[33] in this journal applied the use of acetyl beta-methylcholin to vasospastic disease by iontophoresis. This method does not permit definite knowledge of the dosage given. How much of the drug is absorbed into the skin and how deeply it penetrates remains for future

investigation. The effect is considered to be due to deposition of the drug in the superficial tissues and a low absorption with prolonged vasodilatation. The skin temperature, where spasm of the peripheral vessels was present, increased 4° to 10° for 2 to 4 hours. The place of this technique in treatment of vascular disease, like that of theobromin, is still doubtful.

Barker and Brown,[34] also in this journal, have reported a definite lengthening of time necessary to produce intermittent claudication during a standard claudication test in 92% of 55 cases of thromboangiitis obliterans and arteriosclerosis obliterans following the intramuscular injection of a pancreatic tissue extract. Similar effects were noted in 8 cases of thrombo-angiitis obliterans after intramuscular myoston, a skeletal muscular extract. Myoston, however, was beneficial in only 1 of 5 cases of arteriosclerosis obliterans. In the cases benefited no significant rise in skin temperature was noted, indicating that the results were not due to vasodilatation but, to theorize, probably through supplying some substance to actively contracting muscle, the result of direct action on the ischemic muscle.

Starr[35] also in this journal investigated the effect of three factors, heat, desiccation and oxygen, in the treatment of peripheral vascular disease, especially in acute occlusion. He found, with the use of a constant temperature foot cradle, that the optimum temperature for relief of pain was 33° to 35° C., approximately that of the skin in the lower extremities when vessels are fully dilated. Higher temperature, which might be beneficial to a foot with a normal blood supply, often caused intense pain. The temperature range 33° to 35° C., Starr believes, acts when the normal mechanism is lost by keeping the temperature of the tissues at the level at which they are accustomed to function. While use of oxygen applied locally can relieve pain and change skin color, through its penetration of the skin, results were insufficient to advocate its routine use.

Vasomotor Denervation. Besides the general principles of avoidance of injury and infection, warmth, baths, exercises, use of drugs and other procedures mentioned previously, those procedures described in diagnosis of spasm have been used to relieve vasospasm for therapeutic reasons. The simpler of these methods are more valuable in demonstrating results which can be made permanent by the more serious techniques, such as ganglionectomy and sympathectomy. Brown, Craig and Adson[36] have recently reviewed the criteria for selection of cases for these more serious operations. They reëmphasize that the rationale of the use of operation on the sympathetic nervous system in occlusive disease is based upon previous demonstration of high degrees of vasoconstriction in the non-occluded major and collateral vessels. Use of ganglionectomy depends almost entirely upon proper selection of cases on this basis. The other factor is the clinical aspect of the case. Emphasis is also placed upon the fact that thrombo-angiitis obliterans is a disease with a variable clinical course and after ganglionectomy thrombosis may continue to occur, for there is no definite proof that such operations prevent its occurrence.

While Brown, Craig and Adson state that in 8 years of use they have had conclusive demonstration of maintained and permanent vaso-

dilatation of the peripheral arteries with ganglionectomy, Smithwick, Freeman and White[37] have observed recurrences of vascular spasm after complete sympathectomy in Raynaud's disease. They do not attribute the results to a local fault as Lewis has described it, but believe from experimentation that the vascular spasm is a result of sensitization to adrenalin of the sympathectomized extremity. In these cases care was taken to insure a complete interruption of the sympathetic pathway so that the results cannot be explained on incomplete surgical interruption of the pathways, nor on regeneration. Results were more permanent in the lower extremities. Reappearance of symptoms occurred on exposure to cold and also in response to pain and emotional stimuli, which suggested the possibility of a direct action of adrenalin upon the bloodvessels. Hypoglycemia, which also mobilizes adrenalin, produced the same results. Intravenous adrenalin in doses which produce in the blood a concentration similar to that in physiologic response of endogenous adrenalin caused a rapid fall in surface temperature in the sympathectomized extremity. The normally innervated or partially sympathectomized parts showed no remarkable changes. Further work on animals is necessary to establish the results and to explain the discrepancy between results in the upper and lower extremities.

Parathyroidectomy. Bernheim and Garlock,[38] as a result of observations to be reported later, have formed the opinion that calcium metabolism is an important factor in Raynaud's disease and other vasospastic states. A mechanism of production of vasospastic phenomenon by defective calcium metabolism is not evident. They have subjected 6 patients with Raynaud's disease and scleroderma to parathyroidectomy, who were not benefited by conservative treatment. Following operation they noted marked relief of symptoms. Pain was relieved and skin color changed within 24 hours, the best results occurring in uncomplicated Raynaud's disease. In scleroderma the skin became noticeably softer with partial return of function in fixed joints.

Suction and Pressure in the Therapy of Peripheral Vascular Disease. Until recent months, in the absence of spasm in occlusive disease of the arteries, there has been no method by which blood flow could be increased. True, attempts have been made. Ligation of the venous return had been the subject of investigation. Brooks and his associates[39] had continued their work upon this subject. Although they had shown previously that ligation of the vein decreased the blood flow, results also showed a reduction in the percentage of gangrene in experimental animals. This work was extended to patients.[40] In 2 cases of localized arterial obstruction with gangrene marked improvement resulted. In 14 cases due to arteriosclerosis results were favorable in some instances but they believe that favorable results will be obtained only in a small percentage of carefully selected patients.

Suction in the treatment of peripheral vascular disease dates back many years; probably the best known work being Biers' hyperemia by suction.[41] In 1933 two groups in this country, Landis and Gibbon[42] in Philadelphia, and Herrmann and Reid[43,44,45] in Cincinnati, independently published methods to produce changes in pressure over the extremity. Landis and Gibbon based their studies upon the sound

physical principles embodied in Poiseuille's law of the behavior of fluids in rigid tubes. Poiseuille's law states:

$$Q = \frac{\pi P R^4}{8 n L}$$

Q = volume flow per unit of time
P = pressure
R = radius of tube
n = coefficient of viscosity
L = length of tube

It can be seen from this formula that volume flow is directly proportional to the differential pressure. If, then, an artery approaches a rigid tube and one cannot increase blood flow by dilating the vessel, an increase in the differential pressure will increase the flow to the periphery. It would be possible then by increasing the differential pressure to increase the blood supply to the extremity in those cases which heretofore had been considered hopeless. Work by Landis and Gibbon upon arterial schema supported this view[42] and experiments upon humans showed that the digital skin temperature could be raised in this way in normals and in advanced organic vascular disease.[46] Alternate suction and pressure were used with relatively brief periods of suction (−80 to −120 mm. Hg for 25 seconds) and brief periods of pressure (+60 to +80 mm. Hg for 5 seconds). Further work with this method has recently been reported.[47] Treatment is carried out for 2 hours twice daily and longer as the patient requires it. Most of the cases treated were first tried conservatively with other usual methods without benefit. The authors feel that the method is worthy of trial where ordinary means are ineffectual. Thus with help, temporarily, patients are carried over bouts of pain and ulceration, giving time for collateral circulation to develop. Results show a diminution in cyanosis, abolishment of the rest pain of ischemia, and healing of trophic ulcers. Intermittent claudication becomes milder and tolerance to exercise is increased. Contraindications to use of the method include active or spreading cellulitis and encapsulated pus in the part. Too small a number of cases have been treated to permit generalizations as yet.

The work of Herrmann and Reid[43-45,48,49] has progressed simultaneously with, but independently from, that of Landis. They at first used negative pressure alone in cycles lasting 5 minutes, but have shortened them until at present four cycles are completed per minute. The pressure changes have been changed to −80 mm. Hg and +20 to +40 mm. Hg with 5 seconds for the positive and 10 for the negative phase. Treatment periods have been lengthened from 30 minutes to 1 to 2 hours. More recently Herrmann[49] has added 80 to 100 short oscillations per minute to the cyclic changes so that lymphatic and venous obstruction may better be treated. Herrmann and Reid have called their method Pavaex (pa-ssive, va-scular, ex-ercise). A commercial unit is available.

The technique of alternate suction and pressure has been successful in the hands of both groups. In a recent report of Herrmann and Reid[49] results in arteriosclerosis are given. Since results seemed to depend upon the part of the arterial system affected diagnosis was extended by special procedures to localize the sites of greatest clinical importance

in each case. Seventy-five cases were divided into three groups: (1) predominant involvement of the major arteries; (2) cases with little or no knowledge of disease until trivial infection (about one-half of these were diabetics); (3) predominant involvement of the arterioles of the feet. In the first group, 10 cases, with acute or subacute thrombosis of a major peripheral artery, all had complete relief of all major symptoms. In Group 2, 46 cases (43.37%) were completely relieved, 47.83% greatly improved and 8.69% with gangrene required less radical amputations than would have been done without the treatment. In the third group, 19 cases (only 15.7%) were relieved, 42.1% were definitely improved and a like number obtained no relief.

Progress in the diagnosis and treatment of peripheral vascular disease is well summed up in the closing remarks of Reid[50] in his Matas Lecture on Vascular Surgery; "Means for estimating peripheral vascular efficiency are almost as accurate as the means of estimating the efficiency of the bloodvessels of the heart and kidney. They are waiting to be put into general use by our profession. Once it becomes the practice to study the peripheral vessels and to advise people when there is a thin margin of safety in the blood supply of their legs, there are many things that can be done to avoid those critical periods of pain, infection, gangrene and amputation. Then, too, there will be a noticeable diminution in the number of patients treated for cramps, metatarsalgia, fallen arches and rheumatism."

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(Titles have been omitted for sake of brevity.)

PEDIATRICS

UNDER THE CHARGE OF
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THE DIAGNOSIS AND TREATMENT OF PERTUSSIS.

Pertussis is a disease which too often has been regarded as trivial. Parents are prone to pay little attention until the paroxysms have become severe. Even then many will manifest a philosophy of the Stoic so long as they themselves are not the sufferers knowing that in the majority of instances that a period of subsidence will develop and that sooner or later the patient will recover. On the other hand some parents will seek their physicians in an attempt to secure relief for the little patient. This is not always easy nor prompt, as experience has shown that relief is more difficult in direct ratio to the length of time that the condition has progressed. All in all whooping cough is one of the most unsatisfactory of diseases to treat. Consequently the differences of opinions of physicians in regard to the efficiency of the different therapeutic measures are as variable as the number expressing themselves. Some of the procedures used will be enumerated later and the viewpoints of certain observers will be given. From both the epidemiologic and therapeutic aspects the greatest difficulty arises from the fact that at its onset pertussis presents the same clinical picture

as acute rhinitis or acute bronchitis or the pre-eruptive stage of certain of the exanthemata. Except in the presence of an epidemic or with a history of contact with a known case, suspicion of whooping cough may not be aroused until the end of the second or the beginning of the third week, when the cough becomes more exaggerated and more paroxysmal in type. More recent efforts with the problem of pertussis have been in attempting to improve a method for earlier diagnosis and also in the development of a prophylactic material for the immunization of infants and young children. As will be shown later, encouraging results have been observed, and it is to be hoped that widespread immunization will be as successful in reducing epidemics of pertussis as it has of diphtheria.

The picture of pertussis as an acute infection with or without complications seems to be misleading according to Cockshut.[1] He suggested that pneumonia is often not a complication in the true sense, but a terminal condition. The patient may die or may recover according to the severity of the original infection, the powers of resistance of the patient and similar factors rather than to the extent and severity of the so-called complications. Whooping cough, at least in its severest form, should be regarded as an acute generalized infection. The ordinary course of the disease is one where the whoop is the dominant feature and the patient remains essentially well throughout the illness. In the severe type the patient is seriously ill from the beginning. Although the latter group requires all the benefits of therapeutic development, the milder forms also require active treatment, because even these are very distressing.

The result of vaccine treatment of pertussis has been very good in the hands of some practitioners, but in the hands of others, apparently in the majority, the results have been most disappointing. Because of this all vaccines for pertussis were omitted from New and Non-official Remedies in 1931.[2] In the 20 years that have elapsed since the first introduction of such a vaccine, no conclusive evidence has been accumulated regarding the therapeutic efficacy of such preparations. The Council held that it was not warranted in retaining pertussis vaccines in New and Non-official Remedies. Notwithstanding this conclusion and action these preparations in the hands of many physicians gave results that were entirely satisfactory both as prophylactic and active methods of treating this most distressing and often most dangerous disease. Bivings[3] found pertussis vaccine to be an effective agent in the treatment of whooping cough and even more satisfactory as a prophylactic method. Undoubtedly he struck the keynote of the situation when he emphasized that the vaccine must be given in large doses to secure maximum results, as a few large doses were far more effective than many small ones. He rarely gave more than 4 doses, and in the few instances that he exceeded this number it was only to give 2 additional doses so that 6 doses were the greatest number of doses that were given. His procedure was to give an injection every other day beginning as soon as possible after establishing the diagnosis. In addition to giving too small doses, absence of satisfactory response has been due to the intiation of treatment being delayed until the disease has become too well developed, for the later in the course the treatment is started the more difficult it is to bring the paroxysms under control.

To avoid this in doubtful cases Bivings recommended the use of the mixed vaccine as no harmful effects ensue and in event the cough is not pertussis, immunity of several months' duration against pertussis is established. In children from 2 to 6 years he commenced with 0.5 cc. for the first dose, 1 cc. for the second, 1.5 for the third and 2 cc. for the fourth. When additional doses were given he used 2.5 cc. for the fifth and 3 cc. for the sixth doses. In the last 2 doses one-half of the quantity was injected into each arm or the entire amount between the scapulæ.

Schowalter[4] studied the statistics of 16 years from the Milwaukee County Home for Dependent Children. During the first half of this period no vaccine was used, while during the second half of the period all children under 6 years received either pertussis vaccine or pertussis ectoantigen upon admission to the institution. In this manner over 2700 children received prophylactic injections. In the first period when no vaccine was used, there was 1 year during which no cases of whooping cough developed, and another year during which the number totaled 56. The morbidity rate during this period was 67.5 per 1000 children and the mortality rate was 4.9%. During the period when the vaccine was used the morbidity rate 136.4 per 1000 children and the mortality rate was 2.9%. It is of interest to note that during the same periods in the city of Milwaukee the morbidity rates for pertussis were 255.5 and 384.7 respectively per 100,000 population. and the mortality rates were 2.8% and 0.8% respectively. Thus, while the incidence of the disease was greater during the second period, either the severity was less or treatment was of some benefit.

The therapeusis of pertussis covers a wide variation of remedies and procedures. Emetics, antispasmodic cough syrups, special preparations such as pertussin and diatussin and many other things have been used in attempts to lessen the severity of the paroxysms and to shorten the course of the disease. Ether has been recommended administered by subcutaneous injection or by rectal injection in olive oil. Wildtgrube[5] recommended the use of a concentrated vaccine made from Bordet-Gengou bacilli given as early as possible. He commented, however, that just as good results were said to be obtained with injections of milk.

Lewis and Barenberg[6] gave their experiences in regard to the prophylactic effect of normal whole adult blood on the course of whooping cough. Of 17 children exposed to this disease, 6 were given 30 cc. of whole adult blood and 11 served as controls. All of these children were in one ward and under the same conditions of diet, hygiene and nursing care and as all had been exposed to the same source of whooping cough, comparative results should be of considerable accuracy. All of the 6 children who received blood developed whooping cough, which, however, was of lesser severity than in the control group. Of the 6 children so treated the course of the whooping cough was mild in 5 instances and moderate in 1 case. On the other hand of the 11 untreated children, 2 had mild cases, 3 had moderate cases and 5 had severe cases. It was necessary to administer codein to 3 of the severe cases in an attempt to reduce the number and severity of the paroxysms. The authors claimed that the results following the inoculation of whole adult blood were definitely superior to those obtained with the use of pertussis vaccine. The use of the dry Lyophile serum of pooled human blood, as

developed by Flosdorf, Mudd, *et al.* and procurable at the Philadelphia Serum Exchange of the Children's Hospital, greatly simplifies the application of such treatment.

Epstein[7] called attention to his previous report in the same periodical in 1932, in which he recommended the use of gold tribromid in the treatment of pertussis. In this later paper he reported a study and observation of 150 cases of whooping cough in children, two-thirds of whom were treated with gold tribromid and one-third, used as a control, were treated with the usual antiwhooping cough remedies. Using elixir of gold bromid in 100 children he noted that after 3 or 4 days the cough became less frequent and less distressing, the attacks were milder, the vomiting ceased and the sleep was more restful. Out of the 100 children 69 were entirely well at the end of 4 weeks, 17 at the end of 5 weeks and 14 at the end of 6 weeks of treatment. On the other hand the 50 children who were used as controls and who were treated with the usual antipertussis drugs did not fare so well. No improvement was noted until the end of the second week. Of this control series 24 were entirely well at the end of 10 weeks, 18 at the end of 13 weeks and 8 at the end of 15 weeks of treatment. The use of vaccine in 20 cases and ether in 5 did not materially influence the results.

Ellstein[8] employed many drugs and also the vaccines with most unsatisfactory results. He treated 30 children with gold bromid and was greatly pleased with the results. In 20 cases the cough subsided in 3 weeks; in 7 cases, in 4 weeks; in 5 , in 5 weeks. In all of these 30 children, after 2 or 3 days' treatment with gold tribromid, the cough was less severe, vomiting ceased and the children slept better. The dose of the Elixir Bromaurate was a teaspoonful 3 or 4 times a day after meals, or more often when necessary to control the cough paroxysms.

Barbour[9] claimed beneficial effect in certain cases of pertussis from the administration of whole suprarenal gland. He treated 192 patients with desiccated whole suprarenal gland given by mouth at regular intervals either throughout the course of their illness or from the time he first attended them until the cough ceased. Fifty-six of the cases did so well that he used no other remedy. He found that the maximum dose required was from $\frac{1}{2}$ to 1 grain for infants and from 1 to 2 grains for children. Better results followed the administration of the suprarenal extract when given at 2 or 3-hour intervals than larger doses at longer intervals. In 38 cases thyroid extract was added. In another group of 58 cases a foreign serum protein was used. In 40 cases commercial pertussis vaccine was used with the suprarenal medication. From his observations in this study he believed that by combining the use of whole suprarenal gland by mouth and occasionally with thyroid extract and some form of serotherapy a marked decrease in the severity and duration of from 80 to 90% of the cases of whooping cough may be produced.

Weisberg[10] reported a series of 116 cases of whooping cough treated with tussiva. This contains tincture of bryonia, tincture pulsatilla, eucalyptus and golden antimony sulphid in a concentrated solution. In his routine the parents were advised in regards to hygiene and diet. His remedy was given 1 teaspoonful in about 5 ounces of water and 1 teaspoonful of this mixture was given every hour so that the patient

received 14 or 15 doses in 24 hours. Infants under 2 years of age received half doses, but occasionally it was deemed advisable to alternate a full dose. The product was readily taken and the author felt that definitely good results were produced.

In any of the many methods of treating pertussis the same handicap is encountered because of the difficulty in diagnosing this condition in the early stage except in epidemics or where there has been a known and definite exposure. A fairly early diagnosis may be made by leukocyte count. A leukocytosis associated with a persistent cough especially when showing a preponderance of lymphocytes is a fairly conclusive evidence of pertussis. The complement fixation and the agglutination tests have been used for diagnosis. Neither have been very helpful but of the two the former showed better results. An early diagnosis may be made with the cough plate method. Sauer[11] stated that a positive plate is indisputable evidence of pertussis, but negative plates do not exclude the disease. The same author[12] in a total of 470 cases isolated the Bordet-Gengou bacillus from 88% in the catarrhal stage, from 68% in the paroxysmal stage and from none in the stage of decline of the disease. This observation showed the value of this method in the diagnosis of this disease during the early period when ignorance of its presence and carelessness in making contacts favor the development of large epidemics. This method should be of very great value in the treatment and control of pertussis. A plate culture taken as the patient begins to show improvement will establish the time at which the patient is no longer a source of dissemination of the disease. Sauer[13] gave in some detail the technique of preparing the culture medium and of exposing the plates, as well as the methods of incubation and interpretation of the cultures. To the general practitioner or pediatrician not having access to a properly equipped laboratory this method is of no practical value. As a refutation of the last statement Kendrick and Eldering[14] described how their laboratory findings have been applied in the Grand Rapids Health department in a program of whooping-cough control. The exposure of the cough plates was done almost entirely by 25 nurses in the Bureau of Public Health Nursing. Upon the request of a physician the nurse in the particular district secured a diagnostic cough plate, and the laboratory findings were reported both to the physican and to the City Health Department. If the first plate was negative or unsatisfactory and the diagnosis of whooping cough had not been ruled out in the meantime, a second plate was obtained. While only 22 physicians availed themselves of this service during the first year, there were 70 users during the second year. Another phase of this method according to the authors is its use in releasing from quarantine restrictions cases which have became negative bacteriologically as was mentioned previously.

City, State and Federal reports show that whooping cough differs from other contagious diseases in that nearly all of the deaths occur before the third year of life. Whooping cough is relatively benign after infancy. This epidemiologic fact emphasizes the urgency for attempts at eradication of the disease during the early years of life and warrants an immunization especially of infants and children less than 3 years of age. The Bacillus pertussis vaccine used now over a period of $5\frac{1}{2}$ years differs from other vaccines used for pertussis. In

addition to the older forms of Bordet-Gengou bacillus it contains recently isolated, hemolytic strains of the Bordet-Gengou organism and the preparation is made freshly every few months. Another very important point is that the medium used in its culture contains 20% of freshly defibrinated human blood. Sauer[15] described how the 48-hour growth is scraped off and suspended in physiologic solution of sodium chlorid, containing 0.5% of phenol. After a week the pure, sterile vaccine is diluted to contain 10 billion bacilli per cc. About 650 non-immune infants were given the vaccine before any exposure had occurred. The total dosage after 6 months of age was 8 cc. In administering the vaccine 1 cc. is injected just under the skin in the deltoid region of each arm. One week later 1.5 cc. are injected under the skin in the biceps region of each arm. After another interval of 1 week 1.5 cc. are injected in the triceps region of each arm. The youngest group of children to whom vaccine was administered consisted of 150 infants less than 3 months of age. Each of these were given a total of 6 cc. Their local and systemic reactions were negligible. The age of the main group of non-immune children who received injections in this series of Sauer, numbering more than 500, ranged in age from 6 months to 4 years, the average age being 14 months. Taking all factors into consideration the best age for immunization is between the the seventh and the tenth months. In giving the injection the skin should be cleansed with alcohol and the syringe and needle should be sterilized thoroughly by boiling. Reactions to the injections are chiefly local, although transient rise of temperature may occur in from 4 to 36 hours after an injection. The reactions are due to the bacilli and their products both toxin and endotoxin. The cloudiness of the vaccine is due to the bacilli. The special nature of the suspension is a factor in the slow absorption. A transient local redness, tenderness and induration may be noted in some instances. No reaction in this series was severe enough to necessitate the postponement of the subsequent injection. More than 3500 injections were given without the occurrence of infection at the site of the injection. Each mother was told, just before and after the first injection and after the subsequent injections, that if a local reaction or tenderness should develop she should not be concerned. Local reactions usually reached their peak about 24 hours after the injection, after which the tenderness rapidly subsided. At the time of the subsequent injections a small, circumscribed residual induration of the skin or a subcutaneous nodule might be felt. The persistence of these small nodules was probably due to the slow absorption which results from the toxic action of the vaccine on the subcutaneous tissues. This vaccine contains no foreign serum and will not sensitize, nor will it cause anaphylactic reactions, serum sickness or the phenomenon of Arthus. The active immunity conferred by the vaccine seemed to depend on the potency and the interval of time between injection and exposure. This period should be at least 4 months. Adherence to the technique of administration is of the utmost importance. In this paper Sauer makes no claims for this material as an active therapeutic agent in the developed disease. However, bacteriologic houses are now selling a preparation containing the hemolytic pertussis organism which they recommend for the treatment of the active disease.

Although Sauer seems to have published more papers on this treat-

ment than any other one person, credit for its development belongs to Krueger. The manufacturers call this new preparation Sauer's vaccine yet Frawley, Stallings and Nichols[16] stated that Krueger and Krueger, Nichols and Frawley had recently described a method for the preparation of a new pertussis antigen. This method of antigen production by endotoxin-producing cells such as streptococci, gonococci and Bacilli coli had previously been developed by Krueger. The essential feature of this process is the physical disruption of the living cells with the extraction of the endocellular elements without the use of heat or chemicals and thereby obviating denaturation reactions. In Germany the new, toxin-free vaccine for whooping cough is called "Petein." According to Krueger[17] this was developed by H. Langer from 58 strains of B. Bordet-Gengou of the hemophilus type. In its preparation the greatest care is taken in preserving the presence of a high quota of blood in the medium, and to remove the endotoxin from the bacterial bodies, because of the fact peculiar to whooping cough, it is not the endotoxin that releases the toxin-antitoxin effect, but it is the bacterial bodies that stimulates the formation of the antibodies.

Frawley[18] discussed the results of 2 years' experience in the prophylactic treatment of pertussis. Because of the absence of reactions it is possible to carry out a vaccination program on large groups of children entering school life. Such children are especially in need of prophylactic vaccination as they are at this time most likely to be thrown in contact with the disease. This is much the worst age for contacts, although the infants show a much more serious illness from the disease. Infants are less exposed to pertussis and usually then through older children of the family making contact in school. From the standpoint of preventing epidemics immunization of kindergarten and preschool children is of the utmost importance.

In the treatment of the active case of pertussis several criteria enter into the evaluation of inoculations. The first of these in importance is the quality of the vaccine. The second is the time at which treatment is started and the third is the suggestive component. If inoculation in the organic or infectious stage of the disease in infants or in non-suggestible children stops the vomiting, improves the appetite, reduces the number and the severity of the attacks especially the whoop, and finally checks all coughing within a reasonable time, a specific effect must be granted. Rosenbusch[19] recommended the use of vaccine although his observations were not made with the new vaccine which contains the Hemophilus pertussis. Gundel[20] stated that the so-called polyvalent whooping-cough vaccines heretofore available were mostly non-specific vaccines, consisting for the greater part of B. influenza. He felt that the new development containing Hemophilus pertussis promises to be of great value in the treatment of the active disease in addition to its value as a prophylactic agent.

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PHYSIOLOGY

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Platelets and the Structure of the Blood Fibrin Gel. L. M. TOCANTINS (Department of Medicine, Jefferson Medical College). Platelet-free clots show less rigidity, firmness and contractility than platelet-rich clots. Observations on platelet-rich and platelet-free recalcified oxalated and citrated plasma, heparinized plasma, thrombopenic and hemophilic plasma undergoing coagulation under the microscope, led to the following results and interpretation of the relation of the platelets to the structure and physical properties of the blood gel:

Soon after the fibrin is laid down, intact platelets in the interior of the clot converge toward the fibrin threads, adhere to them, and form firm knots at their intersections. As these knots are formed the threads

become bent, twisted and shortened. By contrast, in platelet-free clots or platelet-rich clots to which antiplatelet serum has been added, the threads are rarely united and remain straight and tense for a long time.

It appears that it is by binding the fibrin threads together at their intersections that the platelets render the clot firm, rigid and elastic. It is perhaps while this is taking place and as a result of it that the clot undergoes the visible reduction in volume (syneresis).

Fibrin does not issue from platelet clumps as generally contended; these clumps form around the previously laid fibrin.

Observations on the Variation of the Diphtheria Bacillus. H. E. MORTON (Laboratory of Bacteriology, University of Pennsylvania). In a study of the diphtheria bacillus from the standpoint of variation, at least four stable colony types were found. By applying the present bacteriologic nomenclature to the colony types, we have the smooth (S), intermediate (SR), rough (R) and dwarf (D) types of diphtheria colonies. A comparative study of these colonial types has shown that many of the heretofore described discrepancies in the behavior of the diphtheria bacillus can be correlated with colony form. It is the SR type which is most frequently encountered and which appears to be the most pathogenic. The S, R and D types are less pathogenic, but not totally avirulent. The SR type shows the characteristic irregularly shaped and unevenly staining cells. The S type shows more regularly shaped and more evenly staining forms. The R type shows more solid staining, shorter and thicker cells and a tendency for the cells to remain attached to one another. Organisms in the D type of colonies are very minute rods. S and D forms give stable suspensions in physiologic saline solution, the R type clumps spontaneously, and the SR type gives intermediate reactions. All types give the same fermentation reactions, there being, however, some quantitative variations. In general, the various colony types show quantitative rather than qualitative variations in the various tests to which they were subjected.

Relation Between Intracellular Acidity and Roentgen Ray Sensitivity. R. E. ZIRKLE (Johnson Foundation, University of Pennsylvania). The Roentgen ray sensitivity of Paramœcium and of the spore of the fern Pteris longifolia is markedly altered by the presence of penetrating acids and bases during irradiation. In the fern spore, increase in concentration of carbon dioxid or hydrogen sulphid first increases and then decreases the radiosensitivity, the range of variation being greater than 1 to 2. Increase in concentration of ammonia first decreases the sensitivity and then increases it. These changes all occur with concentrations that have no effect in absence of Roentgen rays. The sensitivity of Paramœcium is similarly altered, except that smaller concentrations are effective and the effect is complicated by the onset of toxicity of the penetrating acids and bases themselves.

In the fern spore the quantitative relations between intracellular acidity and radiosensitivity are markedly dependent upon the intensity of the Roentgen rays.

Studies on Osmotic Equilibrium and on the Kinetics of Osmosis in Living Cells by a Diffraction Method. BALDUIN LUCKÉ, MARTIN G. LARRABEE and H. KEFFER HARTLINE (Laboratory of Pathology and

Johnson Foundation, University of Pennsylvania). Osmotic equilibrium and kinetics of osmosis of living cells (unfertilized eggs of Arbacia punctulata) have been studied by a diffraction method. This method consists in illuminating a suspension of cells by parallel monochromatic light and measuring, by means of telescope and scale, the angular dimensions of the resulting diffraction pattern from which the average volume of the cells may be computed. The method is far less laborious and possesses several advantages over direct measurement of individual cells. The average size of a large number of cells is obtained from a single measurement of the diffraction pattern and thus individual variability is averaged out. The observations can be made at intervals of a few seconds, permitting changes in volume to be followed satisfactorily. During the measurements the cells are in suspension and are constantly stirred. Volumes of cells in equilibrium with solutions of different osmotic pressure have been determined. In agreement with our previous experiments, based upon direct microscope measurements, we have confirmed the applicability of the law of Boyle-van't Hoff to these cells; that is to say, the product of volume and pres sure has been found to be approximately constant if allowance be made for the volume of osmotically inactive material of the cell contents. The volume of osmotically inactive material was found to be, on the average, 12% of the initial cell volume; in eggs from different animals this value ranged from 7 to 20%. Permeability to water of the Arbacia egg has been found to average at 22° C. 0.106 micron of water per square micron of cell surface, per minute, per atmosphere of difference in osmotic pressure. Permeability to ethylene glycol has been found to average, at 24° C., 4×10^{-15} molecules, per square micron of cell surface, per minute, for a concentration difference of 1 molecule per liter. This is in agreement with the values reported by Stewart and Jacobs.

Studies on the Identification of a Compound Isolated From Scallop Muscle. ELINOR MOORE and D. WRIGHT WILSON (Laboratory of Physiological Chemistry, University of Pennsylvania). Guanidin compounds have long been known as constituents of muscle extracts. Within the past few years two of these, creatin and arginin, have been shown to be present as labile phosphoric acid compounds which are of great importance in muscle metabolism. Recently several invertebrates have yielded guanidin derivatives of unexpected nature. It is, therefore, of interest to find still another member of the series in a compound isolated from the extract of the adductor of the deep-sea scallop.

Analysis of the picrate of this substance for carbon, hydrogen and nitrogen, the only elements present besides oxygen, points to the formula $C_9H_{18}N_4O_4$ for the free compound. The molecular weight found is 240, which agrees with 246 calculated from the formula. Tests and analytical results show the absence of rings. There is no primary amino group, no ordinary peptid bond and no N-alkyl group. The four oxygens are thought to be in two carboxyl groups, one of which is titrated in alcohol. There must be an asymmetric carbon. The presence of a monosubstituted guanidin group is indicated by the acetyl-benzoyl and Sakaguchi reactions and by the splitting off of urea

with barium hydroxid. The monoprimary amin, $C_8H_{16}N_2O_4$, formed by this treatment, yields on oxidation with silver oxid nearly two equivalents of carbon dioxid and one of ammonia and also acetaldehyd, acetic acid and an amin as yet unidentified.

It is tentatively suggested that the compound may be a derivative of arginin, formed by substitution on the α-amino group with propionic acid attached through the α carbon.

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